PRACTICAL ENDOCRINOLOGY

Handbooks for the General Practitioner

PRACTICAL ENDOCRINOLOGY

MINOR SURGERY

PRACTICAL OBSTETRICS

PRACTICAL PEDIATRICS

INFECTIOUS DISEASES

PRACTICAL NEUROLOGY

PRACTICAL DERMATOLOGY

DIABETES

PRACTICAL CARDIOLOGY

PRACTICAL OTORHINOLARYNGOLOGY

Handbooks for the General Practitioner

PRACTICAL ENDOCRINOLOGY

by Lewis M. Hurxthal, M.D.
Head of Department of Internal Medicine, Lahey Clinic

IN COOPERATION WITH

A. Seymour Parker, M.D.
Physician, Department of Internal Medicine, Lahey Clinic

AND

Hirsh Sulkowitch, M.D.
Research Associate, Lahey Foundation

New York

LANDSBERGER MEDICAL BOOKS, INC.

Distributed solely by
THE BLAKISTON DIVISION OF THE McGRAW-HILL BOOK CO.
with the exception of Continental Europe

Manufactured in the United States of America
By the Colonial Press Inc., Clinton, Massachusetts

Designed by Stefan Salter
Library of Congress Card Number 55-8243

PREFACE

The general practitioner is in need of up-to-date clinical information. He wishes to know about diagnostic and therapeutic progress in clinical medicine. He desires to treat his patients and does not always wish to or in many cases cannot refer them to specialists. Despite his needs for medical information, he has little time to read. Even the best available medical books are not especially adapted for use under these circumstances or practical enough for the dissemination of medical advances among general practitioners. Many books are written by specialists for specialists, and are too comprehensive for physicians who have to be orientated about every field of clinical medicine. It is nearly impossible for these busiest of medical men to buy and absorb the enormous volume of specialized publications, which would require reading for their enlightenment.

To fill this need it is intended to publish a series of "Handbooks for the General Practitioner." The books in this series will be written and edited especially for the general practitioner and will reflect the latest developments in diagnosis and therapy, but will not contain elabo-

rate discussion of theory. The material for these books will be short, clear and not too technical in order to be of practical value for everyday practice.

I am pleased that I could undertake the writing of this book on "Practical Endocrinology," which will appear as one of the first books of the series. Although diabetes is an endocrine disorder, the subject will be presented in another volume of this series by Dr. Howard F. Root and Dr Priscilla White of the Joslin Clinic.

Let me say something about the content and classification of this book. General considerations of normal growth and development will precede the discussion of each of the endocrine glands. Many endocrine or pseudo-endocrine disturbances in childhood must be differentiated on the basis of a familiarity with what constitutes the wide range of normal development. Each gland and its respective disorders will be presented, along with differential diagnosis. Classical endocrine syndromes are comparatively rare in contrast to the many disorders which may mimic or suggest them. How to separate them is one of the author's objectives in this book. Classification of the syndromes discussed in this book follows the generally accepted and current views.

An endocrine gland's function depends on many variants. Overactivity or underactivity of a gland with one secretion renders classification a simple matter but the glands with multiple hormones, such as the pituitary or the adrenal gland, give rise to more complex clinical syndromes. Tumors of glands which in themselves have hor-

monal activity or may interfere with normal function further complicate classification. Thus, it is possible to have simultaneously overacting of one part of a gland and underactivity of another. In addition, there are the stimulating or inhibiting effects of one endocrine gland upon another.

After the various disorders of each gland are described along with methods of diagnosis and treatment, several special chapters are presented, dealing with hirsutism and gynecomastia, in addition, a review of sterility and a chapter on the therapeutic uses of steroid compounds as well as corticotropin and chorionic gonadotropin. Simple laboratory procedures constitute another chapter.

For more extensive references on clinical endocrinology it is suggested by the authors that the book "Clinical Endocrinology" by Drs Hurxthal and Musulin be consulted (Lippincott, 1950, 2 volumes.)

I wish especially to thank Dr. A. Seymour Parker and Dr. Hirsh Sulkowitch for their contributions.

LEWIS M. HURXTHAL, M.D.
Boston, Massachusetts

December 1954

CONTENTS

CHAPTER VII

CHAPTER VIII

CHAPTER IX

CHAPTER X

CHAPTER XI

CHAPTER I

ENDOCRINE DISORDERS OF INFANCY AND CHILDHOOD

A. GENERAL INFORMATION

Endocrine disorders may begin at any time after birth; in fact, there are several which may be present at birth. They usually can be recognized shortly thereafter by certain abnormalities; I am referring especially to the congenital adrenogenital syndrome which can be recognized in the female by an enlarged clitoris and in the male by a larger penis than would be expected. In the former one might consider the infant to be a male with undescended testes and hypospadias. The adrenogenital syndrome is due to adrenocortical hyperplasia with excess secretion of androgenic hormones.

Roentgenograms of the hands and wrists show an advanced bone age for chronological age even at birth. Urinary 17-ketosteroids can be determined and will be found elevated and confirmatory. Recognition is important in view of successful treatment with cortisone.

CHAPTER X

CHAPTER XI

may be retarded, particularly in cretinism or in conditions in which there is retarded growth; these will be discussed in more detail later.

Teeth

Eruption of the teeth may be at times an important phenomenon. The incisor teeth erupt in from six to ten months, the cuspid teeth from sixteen to twenty months and the first molar from twelve to sixteen months. These are the deciduous teeth. Permanent dentition begins with the incisors which appear between six and nine years, the cuspids between nine and twelve years, the bicuspids between eleven to twelve years in the maxilla, and in the mandible from one to two and one half years. These are the more important times to keep in mind and may indicate any type of retarded growth.

Linear Growth

Linear growth usually proceeds at a fairly normal rate up to the pubescent period, at which time there is usually a spurt. The longer a child measures, or the taller he is, the more rapid rate of growth is to be expected The average male at one year measures approximately thirty inches long and grows a little over thirty-six inches in the next seventeen or eighteen years This growth rate is at the average of about one and one half inches a year, but a little greater in taller boys and a little less in shorter boys. It is very unusual for a child to grow more than two and one half inches a year and this usually occurs in the spurt

Cretinism is another endocrine disorder which may be present at birth but which may not become apparent for three to six months thereafter. The cretinous baby may rarely cry and thus be considered unusually "good." However, the infant may not take its feedings too well and may suffer from constipation. Usually by six to eight months, if the condition is fully developed, it can be recognized by dryness of the skin, the puffiness about the eyes, the somewhat distended abdomen, often with umbilical hernia. Roentgenograms taken of the bones will show a retarded bone age. Thyroid deficiency may occur any time later, when it is called by some infantile myxedema or childhood myxedema; however, the term cretinism is a satisfactory one.

STAGES OF NORMAL DEVELOPMENT

Unless one is practicing pediatrics exclusively, it may be difficult to remember the ages at which certain phenomena occur which indicate normal development. Some idea of the appearance time of perception, crawling, sitting up, standing and walking is therefore necessary to estimate the progress of an infant's growth and development. Detailed data on this subject may be found in any standard textbook on pediatrics; however, a brief review will be undertaken here The average baby sits up at twenty-four to thirty weeks, crawls at thirty-five to forty-five weeks, stands up at fifty-two weeks, and may walk at fifty-six to seventy-two weeks. These phases of development

not unusual, therefore, to find that this may be considerably late in a fair percentage of boys. Some do not show sufficient change or development of these characteristics until the age of sixteen; in fact, there are a few boys of seventeen and eighteen who begin pubescence.

(3) Adolescence in the male may be defined as that stage where there is beginning change in the voice, a decrease in the slight enlargement of the breasts, the appearance of a light beard and mustache, the presence of a good growth of pubic hair with beginning male escutcheon, and the almost mature size of the testes and penis. The prostate, too, may reach normal adult size. Here again the percentages for the delay in pubescence may be projected so that we find adolescence may not be in full swing until the age of eighteen or twenty; in fact, 17 per cent of boys are not in full adolescence until the age of twenty. It is important to realize this because the parents are often unduly concerned, and with uncertainty in the minds of some physicians, treatment may be unnecessarily instituted to stimulate secondary sexual development. Thus, when an apparently physically immature boy between fifteen and eighteen years is observed by the physician, a conservative point of view is advisable. If growth has taken place at an average rate, if the testes are of firm consistency and if after six months or so it can be shown that they are enlarging by careful measurement, it is probable that adolescence will follow in due time.

Should Delayed Adolescence Be Treated? The physi-

beginning with pubescence. Girls, on the other hand, start off with about the same length as boys and on the average grow only about thirty-three inches and usually stop growing by the age of sixteen. They, too, have a spurt at pubescence which is usually a year or so earlier than in males. This increase in growth rate coincides with the development of secondary sex characteristics, such as enlargement of breasts, enlargement of the penis and testes, and the development of pubic hair. Thus it can be seen that if puberty begins late in either the boy or girl, the cessation of growth occurs at a later date than usual.

Puberty and Adolescence in the Male

The variation in the time of onset of puberty is considerably greater than ordinarily recognized. It is for this reason that so many children in the pubescent or adolescent age are considered, especially by their parents, as abnormal.

Various stages of masculine development are as follows:

(1) The prepubescent state which persists in 76 per cent of boys until at least eleven years of age, in 44 per cent until twelve, in 15 per cent until thirteen and in 6 per cent until fourteen.

(2) Pubescence in the male is characterized by prominence of the breasts in many instances, light unpigmented or lanugo hair, early axillary or pubic hair, and increase in the size of the penis and volume of the testes. As may be inferred from the previous percentages, it is

beginning of the school year. These can be scrutinized, but it is more revealing to plot them on graph paper so that the time and amount of growth excess or retardation may be noted in comparison to the average normal growth curves of boys or girls. In cases of retarded growth, roentgenograms of the skull should be obtained to eliminate the possibility of a craniopharyngioma, a tumor which arises in the Rathke's pouch, becomes cystic and may cause pressure upon the hypothalamus or on the pituitary. Craniopharyngiomas most frequently come to light and thus to the attention of parents or physicians between the age of sixteen and seventeen, although they may exert their effect at any time in life.

When growth is retarded it is also advisable to exclude the possibility of thyroid deficiency. A roentgenogram of the wrist will demonstrate the markedly retarded bone age, which along with a low basal metabolic rate and an elevated serum cholesterol (usually over 200 mg) will be sufficient evidence for diagnosis of this condition.

Menarche

The onset of the menarche in females may likewise be retarded and the same general policy should be adopted as was outlined for males. In some girls there may be full secondary sexual development without menstruation This should always make one suspicious of certain congenital abnormalities such as absence of the vagina or uterus, or hematocolpometra. Secondary sexual development in retarded puberty or adolescence in the female may be

cian on the other hand may be under considerable parental pressure to do something about the situation. If, in addition, the boy has become unusually sensitive about his situation, it may be justifiable to administer chorionic gonadotropin to stimulate the Leydig cells of the testes and speed up secondary sexual development. This may be given in doses of 3,000 to 5,000 units subcutaneously each week. If the testes are unresponsive, increased growth of the genitalia will not take place. Under such circumstances, there is reason to believe that some testicular disease is present, which can usually be surmised by palpation of the testes, they are apt to be soft rather than firm, and smaller than one would expect. In such a case, if laboratory facilities are not available to determine an excess of FSH* which usually indicates primary testicular disease, testosterone may be administered which will cause secondary sexual development without further growth of the testes. Response to testosterone, but not to chorionic gonadotropin, is indicative, therefore, of a condition which in all probability will not correct itself spontaneously at a later date (see Eunuchoidism).

Growth Records. When delayed pubescence or adolescence is associated with definite retardation of growth, a different problem exists. Valuable information may be obtained from school records. It is the custom, at least in the United States, to record the weight and height of each child upon entering school and subsequently at the

* Follicle stimulating hormone, a term which also indicates tubular stimulating hormone in the male.

body hair. One assumes that in the normal male closure of the epiphyses results from the testicular secretion of the male hormone. Since the female probably does not excrete male-like hormone from the ovary under normal conditions, and since the administration of estrogen to animals has very little effect upon the epiphyses, it can therefore be deduced that axillary and pubic hair in the female results from either androgenic (or hair-producing) hormones of the adrenal cortex. While the 17-ketosteroid excretion in the urine of both males and females does not show the great difference that one would expect if these steroids represented only the breakdown products of testosterone, it may be concluded that the adrenal cortex of the female secretes hormones of faintly androgenic character, which cause epiphysial closure and the growth of pubic and axillary hair. The rise in urinary 17-ketosteroids in the female at or about the usual age of puberty has been termed the "adrenarche." In the male the rise in urinary 17-ketosteroid excretion is partly the result of androgenic-like hormones from the adrenal cortex as well as the testes so that this term may actually apply to both the male and female. It is of interest that while pubic hair usually appears before axillary hair, a reversal of this process may occur without any prognostic significance.

brought about by the administration of estrogens, but if the patient is of normal height with no gross abnormalities, it is probably undesirable or unnecessary to administer estrogens because, as mentioned above, there is rarely the psychological embarrassment from lack of development in girls as in boys.

There are certain phenomena which have been noted as regards the approach of pubescence which should be mentioned. Pubic and axillary hair, curiously, may develop in girls between eight and nine years without any definite evidence of other secondary sexual development which alone does not mean that there will be a precocious puberty.

Bone Maturation

It might be of interest to consider the factors which cause the epiphyses to unite in the normal male or female. In abnormal conditions, such as the adrenogenital syndrome in either males or females, it is definitely established that there is an excess production of male or androgenic type of hormones from the adrenal cortex in the female as well as in the male. In this condition there is premature closure of the epiphyses so that the entire linear growth may be accomplished by the age of ten, depending of course on the degree of excess androgenic hormones elaborated. At the time of maximum stature in the adrenogenital syndromes, there is in both males and females pubic and axillary hair in considerable quantity; in fact, in both male and female, there may be abdominal, facial and

own experience, I find that the heights measured on the wall at home, or by the various ways in which children are measured at home, are usually worthless. Of course, if measurements have been recorded over a period of six or seven years, there is bound to be a fairly accurate growth curve, but no one measurement can be considered too reliable. Parents often remark that their children have grown three to four inches in a year, or have grown very little. Only a series of measurements, therefore, can have any value. There are several helpful points to remember in determining the height of a child or an adult. First, the patient should be measured without shoes because of the variation in height of soles and heels. Secondly, the height should be measured two or three times, especially noting whether the measurement is made in full expiration or inspiration. If the patient tries to stand erect and takes a deep breath, one may find as much as one quarter to one half inch difference in the reading. In measuring heights, a rigid arm should be used instead of a flexible one on a height measuring contrivance, or, if measured at home, a square object should be used in order to get a right angle from the wall on which the measurement is to be marked. If the patient is tall, there may be a considerable decrease in height during the day if he is up and about. Thus, height should be measured at the same time of day I have seen tall children after being put to bed for a few days actually increase their height by one half to three quarters of an inch. Careful measurements, therefore, are important, especially if one is attempting to

INDEXES OF GROWTH

Inorganic Serum Phosphorus

Growing children have one element in the blood serum which characterizes growth and in all probability represents the effect of the growth hormone of the anterior pituitary gland. This is the serum inorganic phosphorus which in children should be over 5 mg. per 100 cc. when fasting. The reason for this assumption is, first, that it tends to decrease during puberty to the average adult value of about 3 7 to 4 mg. per 100 cc. Secondly, it is found in active acromegaly in which it is known that there is an increase in the growth hormone. Thirdly, the serum inorganic phosphorus in the acromegalic may be decreased by roentgen therapy or surgical removal of the acidophilic adenoma. Furthermore, in pituitary dwarfs or in other dwarfs, such as in cretinism, the serum inorganic phosphorus is below the normal for the chronological age. It is important to obtain blood in the fasting state if this determination is desired because the inorganic phosphorus will decrease after a meal, especially if rich in carbohydrate. A decrease of 1 to 2 mg. per 100 cc. may take place.

Measurement of Height

The determination of the rate of growth of the child is important in considering endocrine disorders. From my

are the three disorders in childhood which will be considered here.

GIGANTISM

The anterior hypophysis is a source of several hormones which control or at least act in reciprocal relationship with other glands in the body. Of most importance in childhood is the growth hormone (somatotropin) which, from a clinical point of view, is active only up to the time of maturity, except in acromegaly where there is a growth promoting tumor of the pituitary gland.

As stated previously, the only evidence we have of activity of growth hormone in childhood is the observance of a normal growth rate over a period of time or an increase in inorganic serum phosphorus at the first or on a single examination. (Other causes for an increased phosphorus duly considered and ruled out, i.e., renal failure, diabetes mellitus, severe hyperthyroidism, hypoparathyroidism.) The serum alkaline phosphatase also increases slightly with increased growth due to growth hormone, and decreases if growth rate is decreased from growth hormone deficiency. In the histories of pituitary giants it can often be determined that the accelerated growth rate took place in childhood, sometimes as early as four or five years of age. The increase of growth rate does not cause much concern in the early stages, because the children are simply considered taller than normal children. When it becomes obvious that the child is excessively tall, then attention is paid to the possibility of

determine the effect of a given medication in increasing height. A series of measurements over a few months is the only safe way to determine a growth rate. Loss of weight of ten to fifteen pounds or more in a child or adult may cause a slight shrinkage in height, and vice versa.

Bone Age

In determining the skeletal age from standard works on this subject, it is well to remember that a retardation of one year or an increase of one year is not too significant, but a difference of two years begins to be of very definite significance as regards skeletal development. Todd's Atlas of Skeletal Maturation, published by Mosby & Company of St. Louis, is undoubtedly the most satisfactory work on the subject in this country.

B. DISORDERS OF THE PITUITARY GLAND IN CHILDREN

Disorders of the anterior pituitary gland in childhood are best represented by the pituitary dwarf and, in rarer instances, the pituitary giant. Cushing's disease may also occur in childhood. The latter condition may be the result of a tumor of the adrenal cortex or adrenocortical hyperplasia, presumably due to an increase in corticotropin of the anterior pituitary. The adrenogenital syndrome due to hyperplasia of the adrenal cortex should theoretically also be the result of excessive secretion of corticotropin of the anterior pituitary, but this is as yet not proven. These

the tumor progresses in size, however, a suppression of gonadotropic hormones may occur after puberty has already begun. If no treatment is carried out at this age, the child therefore may be quite abnormally tall, and if the epiphyses do close, in case the gonadotropic hormones have not been suppressed, the situation may result in acromegalic-gigantism, an intermediate condition between pure gigantism on the one hand and acromegaly on the other.

Should the secretion of excessive growth hormone from a pituitary adenoma occur near the end of adolescence, or shortly thereafter, acromegaly occurs with little or no further increase in linear growth but an increase in the width of bone with the usual enlargement of the hands and feet, prominence of jaw, widening of the bridge of the nose and coarsening of facial features

To return to gigantism which, as stated before, begins in childhood, the giants I have seen have had few complaints. Symptoms are possible, however, depending on the rapidity and extent of growth of the pituitary tumor. Headache, which has no consistent pattern in tumors of the pituitary, and visual change such as decrease in visual acuity or visual field defects, have been present in only one case. It is entirely conceivable that some mental aberrations might occur, aside from somnolence and lethargy. Even convulsive seizures are a remote possibility. Most of these signs or symptoms are late manifestations of the disease occurring at a time when there is little question of gigantism itself. The majority of cases of gigantism begin-

some abnormal situation. Children who are conspicuously tall and over the upper limit of normal stature for their age should therefore have roentgenograms of the skull and sella turcica to see if there is enlargement of this bony compartment which houses the pituitary gland. Pituitary growth hormone in excess does not accelerate epiphysial closure but increases the length of bone and, in some instances, its width. Bone maturation, as previously stated, which indicates "bone age" comes about through the effects of adrenal and testicular steroids in the male and adrenal steroids in the female. In all probability, these steroids are androsterone, testosterone (?) or related androgenic hormones. Estrogens do not have a direct effect on closing epiphyses, so far as is known. Such cases should be observed perhaps for a year or two and accurate measurements of height taken to be sure that there is an increase in growth rate under the observation of the physician. Very little else can be demonstrated in laboratory tests at this age. The diagnosis of pituitary gigantism is a difficult one to make at an early age, but if the sella turcica is at least twice normal size, then this possibility should certainly be considered.

Should a pituitary adenoma be found, say, around the age of ten or eleven, at an early phase of its abnormal secretion of growth hormone, there may be no inhibition of the usual rise of gonadotropic hormones during early adolescence. In such a case there is the usual spurt of growth and development of secondary sexual characteristics if gonadotropic secretion is not interfered with. As

Sella Turcica

The problem of deciding if the sella turcica is enlarged is always a difficult one because of the marked variation in its size in otherwise normal individuals. If average values can be used as a guide, the lateral area of the sella contour measures around 26 to 36 square millimeters in a one year old child, increasing from 45 to 75 square millimeters around ten years of age, and by twenty years of age it is 50 to 100 square millimeters. It is quite possible that a normal individual may have a sella measuring in lateral contour up to 100 square millimeters in late childhood, and even up to 150 square millimeters. Values over 200 in childhood certainly must be considered abnormal, whether any general or local disturbance can be made out. The important thing is to repeat skull films in six months to a year to determine if there is an unusual increase in size, or possibly evidence of pressure, as shown by erosion of the clinoids or a thinning and depression of the sella floor. Enlarging sinuses are important, too.

The size of the sella may increase in gigantism, not necessarily because of an expanding tumor but because of a general increase in size of all structures. Thus, if it does not increase disproportionately in size, this fact does not mean any change in function As will be pointed out later, in acromegalics there may be an increase in the acromegalic process without observable increase in size of the tumor and sella turcica.

There has been so little recorded experience in the treatment of pituitary giants in childhood that we have little

ning in childhood do not develop secondary sexual characteristics. Thus, since the testes and adrenals in the male, or adrenal glands in the female, do not develop as in normal puberty and adolescence, epiphysial closure fails to take place, this being the reason for the excessive and continued growth from twelve years on.

In the differential diagnosis between an abnormally tall boy from fourteen to eighteen years of age and a true pituitary giant, the inorganic serum phosphorus again could be quite helpful. If in such a case there was adequate secondary sexual development and the bone age equivalent to the chronological age, one can exclude further excessive growth, depending upon the stage of puberty or adolescence, but if the sella and frontal sinuses are enlarged and the inorganic serum phosphorus above 4.5 mg. per 100 cc. in this age group, one certainly must think of an overactive pituitary as regards growth hormone and ultimate development of acromegaly if treatment is not carried out.

In the only pituitary giant which the author has personally examined at the age of five, the serum inorganic phosphorus was slightly higher than one would expect at five years of age, and when seen again at nine years, the inorganic phosphorus was 1 mg. higher than in a girl of the same age. Diagnosis was made because of marked enlargement of the sella turcica which increased over a four year period, and of course, because of the abnormal growth rate. Thus, the serum inorganic phosphorus cannot be a conclusive determination at this age, however, it can be used as an index of the effectiveness of therapy.

Stilbestrol has been shown to decrease growth hormone production; at least the serum inorganic phosphorus decreases when it is administered. In our only case in which treatment was begun at nine years of age, 2,500 roentgen units caused cessation of growth rate for only about three to four months. Stilbestrol then was prescribed chiefly because of objections raised by the parents in regard to more x-ray therapy. This was moderately successful, I believe, in retarding growth and keeping the inorganic serum phosphorus below 4.5 mg. per 100 cc. However, x-ray therapy is again contemplated because at the present growth rate, should the epiphyses unite at the usual age, which is doubtful, the girl will be well over 77 inches.

If pituitary gigantism exists when the patient presents himself for the first time after the age of fourteeen or fifteen years, and if there is no evidence of beginning puberty, it is not likely that x-ray therapy will permit a resumption of gonadotropic activity of the pituitary, and hence, puberty and adolescence. However, such is not impossible in view of the return of gonadotropic function in female acromegalics in the menstruating ages. Should there be no evidence of sexual development, then testosterone may be given in fairly large doses in the male, which will close the epiphyses, and ultimately prevent further increase in height Doses of 200 mg every two or three weeks, using long-acting testosterone (depo-testosterone), should be sufficient to do this, but it must be remembered that normally it takes three to four years

to go on as to the best procedure. Pituitary gigantism should be prevented because of the handicap of excessive height in later years. This handicap is both economic and social, since it is almost impossible to purchase clothes and shoes, except for a great outlay of money, and the conspicuousness of the giant and his awkwardness in getting around is undoubtedly most embarrassing.

Treatment

When it is established beyond all doubt that such exists, x-ray treatment over the pituitary should be undertaken. The matter of dosage depends to a great extent on the rapidity of the growth rate. We have found in several instances that a tumor dose of 2,500 roentgen units over the sella may temporarily suppress growth rate, but we do not believe this is sufficient to permanently decrease growth rate to normal. One is concerned about the possible damage of fairly large doses of roentgen rays to the pituitary gland, especially in children, but this fear, I think, need not be seriously entertained. In all probability a tumor dose of 4,000 roentgen units should stop the overactivity of the pituitary tumor and decrease its size. Twenty-five hundred roentgen units may be tried first if there is concern over high dosage and repeated if there is a resumption of growth rate and return of inorganic serum phosphorus to 5 mg. or more per 100 cc. The latter value often falls to about 3.5 mg. a month or so after treatment. It is to be remembered that a tumor dose is about one half the skin dose unit usually used.

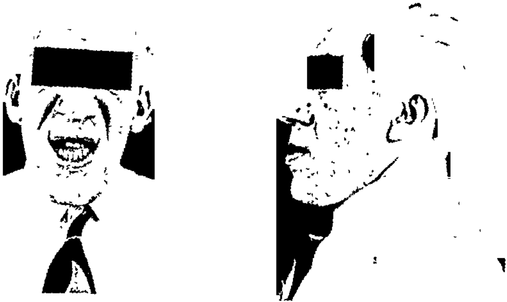


Fig 1 Acromegaly in a young man of 29 Moderate degree of prognathism and prominent frontal sinus bossae *Note that lower teeth override uppers by a considerable margin*

for a child's epiphyses to close upon approaching adolescence. In one giant the author implanted four testosterone pellets, 75 mg. each, every three months or so, and the epiphyses closed in several years, so that had the pituitary adenoma resumed its growth hormone activity thereafter, at least there would have been no increase in height.

If growth hormone excess is stopped by x-ray treatment at a time when the epiphyses are still open, further growth will undoubtedly take place from the use of testosterone because I do not believe the epiphyses can close without some simultaneous increase in linear growth.

In the giant just mentioned, even though there was excessive growth hormone activity, there was little evidence of other pituitary hormone secretion. The patient had a mild anemia, a rather low metabolic rate, and the 17-ketosteroid excretion was only 4 mg. per twenty-four hours. Here was an instance of overactivity of one hormone of the pituitary, and underactivity of the thyrotropic, adrenotropic and gonadotropic hormones.

Should testosterone fail to increase the general strength and stamina of the patient, cortisone may be used in such cases to help out in the general glandular deficiency; 12.5 to 25 mg. a day should be sufficient.

The objective in the treatment of gigantism, from the endocrine standpoint, is to prevent the excessive height and at the same time attempt to permit normal adolescence. Should the giant in the preadolescent period be a female, it is legitimate to administer testosterone in moderate doses, using methyltestosterone in the form of

buccal tablets, 10 to 20 mg. or more a day, to hasten epiphysial closure if there is no evidence of the development of secondary sexual characteristics. This might be a touch and go proposition between avoiding masculinization and closing epiphyses, but it can be withdrawn or reduced should undesirable masculinization begin.

If the menarche is delayed in female gigantism, with little evidence of gonadal function, stilbestrol or other estrogens could be given periodically, followed perhaps by a week of progesterone to cause periodic bleeding. It is the author's conjecture that estrogens may stimulate the pituitary to elaborate adrenocorticotropin and in this way stimulate the adrenal cortex to put out androgenic-like hormones capable of causing bone maturation. The estrogens or stilbestrol is given in doses equivalent to 0.5 mg. of the latter per day for twenty-one days followed by 30 to 50 mg. of anhydrohydroxyprogesterone buccally to cause periodic bleeding.

PREPUBERAL HYPOPITUITARISM FRÖHLICH'S SYNDROME AND OTHER FORMS OF DWARFISM

Hypopituitarism before puberty manifests itself chiefly by a retarded growth rate As in gigantism, the retardation of growth rate may not be noticed until the disorder has been active for two or three years or longer, at which time the child is conspicuously smaller for his age than normal. The term "Fröhlich's syndrome" is frequently applied to fat pubescent boys, particularly those in whom

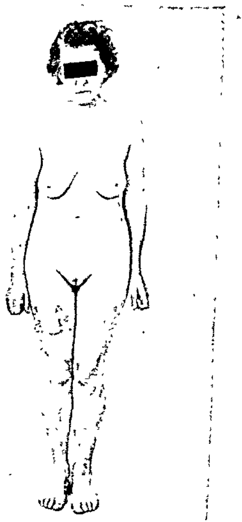


Fig. 2. Simmonds' disease of unknown etiology Loss of axillary, pubic and body hair. Treated originally with testosterone and desoxy-corticosterone pellets, later with a daily dose of cortisone, 25 mg, by mouth

average height for his age, if the bone age is nearly equal to the chronological age, the only immediate therapy advisable is an attempt at weight reduction. Observation over the period of a year will not be in any way detrimental, and one can then observe the increase in size of the testes and penis, along with the normal growth rate. If these changes occur, one can surely predict the onset and completion of a normal puberty and adolescence. In the author's experience, children can lose weight just as well, if not better than adults. The inducement is to make the regime attractive. A suitable reward should be given for weight loss, the equivalent of one pound a week being a satisfactory reduction. The child can be taught to keep his own chart and keep a diary of his food intake. Although there is no statistical evidence to prove that reduction of obesity may stimulate puberty, it is the author's impression that it may hasten this process.

Some believe that it is advisable to stimulate sexual development in cases of pubescent obesity and this can be accomplished by the oral administration of methyltestosterone in doses of 5 to 20 mg. a day, or by the injection of chorionic gonadotropin in doses of 3,000 units subcutaneously weekly. It is doubtful if this is a logical procedure and it is not especially recommended during the pubescent age. (Cryptorchidism and its treatment will be discussed under the chapter on Diseases of the Testes.)

To return to hypopituitarism in children, some investigators question the diagnosis of pituitary dwarfism in the child who is active, alert, strong, yet who shows a

there may be some retardation of puberty, or in whom abundant pubic fat conceals the size of the penis to the extent that it is considered underdeveloped. It is to be remembered in this connection that the testes may remain of infantile size right up to the point of beginning pubescence, at which time they may enlarge. So it is not uncommon to find a boy of eleven or twelve years and sometimes even thirteen, with small testes, which does not indicate testicular disease or underdevelopment. These testes, however, are of fairly good form and consistency, are not mushy or indicative of only a gubernaculum. Fröhlich's syndrome when used in this manner is a misnomer, and one has only to read the original description by Fröhlich to realize that his patient had growth retardation and a suprasellar tumor associated with visual disturbance. Eventually the boy he described became quite obese, but initially this was absent except for a slight female contour of the hips.

Pubescent Obesity

Prepubescent boys, before the androgenic effect of testosterone, may have a very feminine contour and this is not necessarily abnormal The development of obesity in Frohlich's original case was considered to be due to involvement of the hypothalamus by tumor. Some children with craniopharyngiomas are obese, or may be malnourished. Certainly ordinary pubescent obesity cannot be attributed to a hypothalamic disturbance, at least in our present state of knowledge. If the child is of normal

the thyroid deficient child is readily recognized because of the characteristic facial features of thyroid deficiency, yet in the author's experience there is an occasional child who responds to thyroid by a resumption of normal growth rate, yet who is not mentally retarded although he may have a low metabolism, low serum iodine, a high blood cholesterol and retarded bone age (see thyroid chapter).

Diabetic and Nutritional Dwarfism

There are cases of retarded growth in diabetes mellitus. The explanation of this by present day concepts is that growth hormone needs insulin for its effectiveness, and in diabetes of the severe type in which retardation of growth is most likely, there is marked insulin deficiency; hence, growth hormone cannot operate.

Growth may be retarded in other nutritional deficiencies, such as the celiac syndrome, steatorrhea, biliary cirrhosis or von Gierke's disease. There is an intestinal type of dwarfism seen in patients with ileitis or ulcerative colitis. It is also believed that malnutrition resulting from anorexia nervosa may retard growth, although there are few proven examples of this. Recent studies in adults with anorexia nervosa indicate a lowered capacity to use proteins for anabolic processes. Rickets, scurvy and chronic infections may contribute to growth retardation, as well as marked allergic dermatitides or asthma. Experimentally, malnutrition is thought to decrease the secretion of pituitary hormones, and growth may be re-

retarded bone age and is conspicuously short, yet there is often no other diagnosis to make in these cases, after all forms of dwarfism are carefully considered.

Dwarfism

There are several other conditions in infancy and childhood which are associated with retarded growth. The only real definition of a dwarf is a conspicuously short person, and the fact that a child's growth is retarded or in the process of being retarded does not necessarily mean he will end up as a dwarf. Some children, particularly those affected with precocious puberty of idiopathic origin, or those due to overactivity of the adrenal cortices producing the adrenogenital syndrome, may be taller than average for their age, yet end up as dwarfs because of premature closure of the epiphyses.

Primordial Dwarfism

History records innumerable instances of very small individuals, sometimes said to be less than 30 inches tall, yet who developed in every way and were able to reproduce. Not many authenticated examples of this sort exist, and perhaps the most famous dwarf was the celebrated General Tom Thumb, who was certainly a midget and was married to another midget, who bore him a son.

Cretinism

Another glandular condition causing dwarfism, and perhaps the most frequent, is thyroid deficiency. As a rule,

some abnormality is considered. This condition will be more fully discussed under the chapter on ovarian disease.

Mongolism

Mongolism is a congenital condition and is often thought to resemble cretinism; in fact, it is often miscalled cretinism. It may be difficult to recognize this condition in the first six months of infancy because the inner canthus of the eye of the normal infant often persists, suggesting the mongoloid eye. These children behave very much like cretins, however. They tend to breathe through their mouths because of the frequency of adenoids. Other abnormalities are the characteristic ear with flat or absent helix, Darwinian points and a low ear site. There is also retardation of dentition. The characteristic mongoloid appearance eventually is easily recognized and should not be confused with cretinism.

Desiccated thyroid is often prescribed for the mongoloid child In the opinion of those experienced in the treatment of many cases, thyroid may be helpful, perhaps because in some instances there may be concomitant thyroid deficiency. There is little evidence in the author's opinion that it is of pituitary origin, as suggested by some authors.

Laurence-Moon-Biedl Syndrome

Still another cause of dwarfism is the Laurence-Moon-Biedl syndrome, a familial disorder characterized chiefly by syndactylism or polydactylism, atypical retinitis pig-

tarded because of a secondary rather than a primary pituitary deficiency.

Renal, Cardiac and Anemic Dwarfism

Certain congenital kidney lesions, or nephritis or renal rickets may slow down growth rate. Cooley's anemia is another condition in which growth may be retarded. It is well known that children with congenital heart disease may also fail to grow normally.

Progeria

Progeria is another cause of dwarfism. The remark has often been made that "all progeries look alike." They present a characteristic appearance, are thin, pot-bellied, often bald, with peculiar facial expression, suggesting senility. Hypertension and arteriosclerosis are often present.

Ovarian Agenesis

Ovarian or testicular agenesis, sometimes associated with congenital webbing of the neck, termed Turner's syndrome, is associated with growth retardation, but these individuals are usually not too short, and their final height may reach 56 to 57 inches. Few cases of Turner's syndrome in the female have been diagnosed before the usual age of puberty for the simple reason that they are stocky, healthy, and not conspicuously short. It is after they have failed to menstruate and to develop secondary sexual characteristics at the usual time of puberty that

If there is no visual disturbance or other symptoms or signs of intracranial pressure, even though there may be evidence of craniopharyngioma by x-ray examination, it is perhaps best to mark time because no adequate therapy is available to stimulate growth. There may be impingement upon the hypothalamus or the stalk of the *pituitary, giving rise to diabetes insipidus. The presence* of diabetes insipidus with growth retardation should always make one suspicious of craniopharyngioma because it occurs much more in this combination than with any other pituitary tumor. If there is no evidence for craniopharyngioma or pituitary tumor, one then assumes that there is pituitary insufficiency from some obscure cause, possibly congenital defects or infection.

As stated before, the serum inorganic phosphorus in pituitary dwarfism should be below 4 mg., and is more likely to be around 3 mg. per 100 cc. Mild anemia may or may not be present. Determination of the cortisone-like hormones in the urine to date has been so unpredictable that there is little reason to attempt such a laboratory procedure unless facilities are available. Furthermore, it is a highly specialized technique and not suitable for the average routine hospital laboratory. On the other hand, 17-ketosteroid excretion should be far below the average range for age if there is pituitary deficiency.

It is hoped that in the near future, growth hormone may be more effective and available commercially. Results reported so far have been very discouraging, although in 2 female dwarfs reported by Schorr and his associates

mentosa, along with physical signs of gonadotropic and growth hormone deficiency. There is no worth-while treatment for this disorder, unless testosterone be used to develop secondary sexual characteristics—probably an unwise procedure.

Diagnosis

If the above disorders can be eliminated one by one, then we come to the conspicuously short person with markedly retarded bone age, failure of sexual development which, however, before puberty is not inconsistent with the child's chronological age. Such cases should always have a roentgenogram of the skull, particularly to demonstrate calcification caused by craniopharyngiomas in or above the sella turcica. Craniopharyngiomas may be present without calcification, in which case other evidence of an intracranial lesion such as displacement of the pineal must be looked for. The sella, too, may or may not be enlarged from suprasellar pressure or extension of the tumor. Craniopharyngioma may cause pressure on the pituitary or hypothalamus and result in retardation of growth and sexual development. As a rule, however, craniopharyngiomas do not become manifest to the point of causing clinical symptoms much before the age of twelve, although we have seen them as early as five years of age. Unfortunately, the slowing down of growth or failure of sexual development is not usually the reason for seeking medical advice, but headache or visual disturbance causes the parents to consult the doctor.

but if the testes show growth over a period of six months to a year and if the bone age is not remarkably retarded, say, one or two years behind schedule, it is distinctly probable that a child of this sort will have a spurt in growth and puberty at a later date. Children at the usual age of puberty may vary five or six years in general somatic development but, as a rule, the bone age is not so markedly retarded. Then, too, in the boy with delayed pubescence, school records will show a fairly uniform increase in growth rate every year, whereas in the pituitary dwarf, growth will be found to have proceeded very normally until the time that growth retardation sets in, and then the growth rate may be remarkably slowed. In plotting out some of these curves, the falling off of the growth rate curve is readily noted. (For discussion of the treatment of eunuchoidism, see chapter on Diseases of the Testes.)

The indications for treatment of craniopharyngioma are headache, signs of intracranial pressure and visual disturbance. Surgery perhaps is the best procedure if a competent neurosurgeon is available and the cyst is not too large to be removed, as shown by air studies. It is known that in some instances a craniopharyngioma may respond to x-ray. The latter should be reserved for cases in which there is no urgent need to relieve pressure. X-ray therapy in itself may cause edema of the tumor and rapid change in vision, so x-ray should not be used if there is reason to believe that marked pressure effects with visual loss are present.

there was a definite effect of growth hormone. It has been ineffective in about 8 other reported cases.

Treatment

It is worth while trying desiccated thyroid in 1/4 to 1 grain doses, depending on age. The main reason for trying thyroid is that there might be thyroid deficiency without presenting the full clinical manifestations of cretinism or infantile myxedema. Thyroid deficiency may cause retardation of growth, not only because of the lack of thyroid in the tissues and epiphyses, but also because there is reason to believe that growth hormone of the pituitary depends on the normal secretion of the thyroid gland. Experimental work has shown that a thyroidectomized animal loses the eosinophilic cells of the anterior pituitary, from which it is believed with considerable certainty that the pituitary growth hormone is secreted.

Methyltestosterone or testosterone propionate, or depo-testosterone, may be tried in the child approaching ten or eleven years of age because testosterone may cause a spurt in growth, but it will also cause sexual maturity prematurely if it is given at this age and in sufficient quantity. It is often difficult to decide when to try testosterone, but perhaps the best policy is to wait until the age of twelve or thirteen, although it can almost certainly be predicted that a dwarf will not suddenly start to grow if the retardation of growth is of pituitary origin. A good many boys go through puberty rather late and at the age of twelve or thirteen may be considered short in stature;

sufflation of powdered posterior pituitary gland. This may be satisfactory, but in many instances the patient becomes allergic to it, developing congested nasal membranes and even asthma. Pitressin tannate in oil is the most satisfactory preparation on the market and must be given intramuscularly in doses of 0.5 to 1 cc. every twenty-four to forty-eight hours.

CUSHING'S DISEASE OF CHILDHOOD

Cushing's disease may occur in childhood. It is extremely rare and has to be differentiated from the adrenogenital syndrome. These two conditions demonstrate the difference in the adrenal cortical secretions. Cushing's syndrome is largely the result of excessive cortisone-like hormones, whereas adrenogenital syndrome is associated with excessive androgenic or male-like hormones.

Cortisone-like hormones cause the typical rounded face of Cushing's disease; there may be some increase in hair growth; the epiphyses are retarded due to the fact that the cortisone is antagonistic to those hormones which cause epiphysial closure. In addition there may be some osteoporosis, there may be diabetic tendencies, and there may also be some hypertension. Acne occurs in both syndromes.

From a practical and clinical point of view, the simple procedure of doing a very careful differential count of the blood with Cushing's disease should be a satisfactory method of determining whether or not there is overac-

If the pituitary dwarf presents himself at the age of fourteen or fifteen, or thereafter, the only practical treatment at present besides a trial of thyroid is the administration of testosterone, orally, buccally or intramuscularly. Chorionic gonadotropin can be tried and it will stimulate the testes to production of testosterone and secondary sexual characteristics as well as growth. However, few patients like to continue this form of therapy unless there is a great desire for the possibility of spermatogenesis. The latter is extremely unlikely and eventually the patient will prefer to be treated with testosterone. If there is evidence of marked hypopituitarism at this age, which is most likely to occur after the age of fifteen, then one can employ cortisone in doses of 12.5 to 25 mg. a day; testosterone can be used along with cortisone, and desiccated thyroid can be added later in doses up to 1 grain a day, rather than administering it initially.

In the female, however, little can be done unless growth hormone becomes available, and one has to be content with the administration of estrogen. This will cause breast development, and if there is functionable tissue in the pituitary, it may stimulate the adrenal cortex and eventually sexual hair. Periodic bleeding has no particular value, other than psychological. Stilbestrol or other estrogens can be given for a period of twenty-one days, followed by the buccal administration of progesterone or anhydrohydroxyprogesterone. When bleeding ceases, the cycle of treatment can be repeated.

Diabetes insipidus when present can be treated by in-

ing's disease is due to the tumor, it can be safely removed and the patient sustained on cortisone, in fact, be prepared with cortisone before operation and if the other adrenal tissue resumes function, it can eventually be discontinued.

If it has been demonstrated that there is no tumor, and this can only be done by careful air insufflation of the adrenal gland, or if facilities are available for determination of the urinary steroids, tumor can be suspected by the excretion of a large amount of dehydroisoandrosterone. Another practical procedure if urinary hormones can be determined is the administration of cortisone in 50 to 100 mg. a day (preferably parenterally) which, if the condition is due to adrenal hyperplasia, will depress the output of 17-ketosteroids, but it may not do so in the presence of tumor.

With tumor satisfactorily eliminated as the cause of Cushing's disease, x-ray therapy to the pituitary is warranted, providing adequate dosage can be delivered to the pituitary without skin damage. It is estimated that at least 4,000 *roentgen tumor dose units should be used.* If unsuccessful, adrenalectomy may have to be resorted to.

Some authors advocate total adrenalectomy in adults with Cushing's disease since they can be maintained very satisfactorily on cortisone, or cortisone and desoxycorticosterone; 12 5 to 25 mg of cortisone daily is usually sufficient. Desoxycorticosterone is rarely necessary.

tivity of the adrenal cortex as regards cortisone-like hormones. In childhood up to the age of ten or eleven, *there is a relative lymphocytosis*, usually up to 50 per cent. In adults the usual lymphocyte count is around 35 per cent of the total. In adults with active Cushing's disease the lymphocyte count is usually below 15 per cent and often 10 per cent. Thus, if Cushing's disease affects the child, the lymphocyte count should also be correspondingly reduced. If facilities are available for careful total eosinophil counts, one can expect a very low or *absent eosinophil count in Cushing's disease.* As stated before, the estimation of cortisone-like hormones in the urine is still not a practical procedure in clinical laboratories but when it is possible to do this, there should be an elevation of this type of urinary steroid excretion as well as a relative increase in the 17-ketosteroids in the urine. Roentgenograms of the skull show nothing abnormal, except possibly osteoporosis. Roentgenograms of the pelvis may show some decrease in calcification and, as said before, the bone age is also delayed, depending on the duration and severity of the disorder.

Treatment

The treatment of Cushing's disease in the child is dependent on whether *the excessive secretion of cortisone-like hormone arises from a tumor of the adrenal gland, or whether it is associated with hyperplasia.*

The *treatment of Cushing's disease now is much more satisfactory since cortisone* has been available. If Cush-

become too small, or change the size of the gloves or shoes.

Perhaps one of the first abnormalities to be noted in acromegaly is the cessation of the menstrual periods in the female; however, some women with acromegaly continue to have normal menstruation, get pregnant, and go through pregnancy without complication. As a rule, in these cases there is only moderate enlargement of the sella.

Headache may be a symptom and in a certain number there may be disturbances of vision with bilateral defects in the visual fields.

ONSET

The symptoms and the rapidity in the physical change in acromegaly depend to a certain extent on the intensity of the underlying process, namely, excessive growth hormone secretion. There are certainly some cases of acromegaly of very mild degree in which the physical changes are so insidious that it may be as long as ten years before anything unusual is noted. During this time there may be various complaints, such as back ache, mild headache, perhaps increase or decrease in sexual activity. In some cases, on the other hand, the rate of growth and change may be fairly rapid and there may be an associated increase in thyroid function with clinical hyperthyroidism, including the usual tachycardia, increase in pulse pressure, tremor, sweating, and increase in appe-

CHAPTER II

DISORDERS OF THE PITUITARY GLAND IN ADULTS

ACROMEGALY

Acromegaly by definition is enlargement of the acral parts. It is a disorder occurring after epiphysial closure; thus there is no further increase in height but a widening of the bones of the skeleton and often an increase in the length of the jaw oı prognathism.

It is almost invariably the rule that a patient with acromegaly does not consult a physician in its early stages because the changes are unrecognized even by those about them. One who has not seen the patient for several years or more may be the first to comment that there has been a change in the patient's facial features. Enlargement of the hands and feet also may not be noticed unless it becomes necessary to enlarge a ring, having

hormone preparations. This action might be through the liver, in some way rendering possible the synthesis of protein necessary to produce tissue and muscle growth.

It is not an uncommon observation to find that acromegalics have considerable osteoporosis of the bone and occasionally secondary changes such as compression of vertebrae. This loss of calcium from the bones is not adequately understood, it may be present without excessive thyroid or parathyroid function. Kidney stones may occur because of this.

Hypertrophic changes in the bones are a fairly regular feature of long-standing acromegaly. Multiple exostoses may cause orthopedic difficulties occurring in the long bones as well as in the skull.

BLOOD PRESSURE

Hypertension is often thought of as a feature of acromegaly, but in all probability it is an unrelated and coincidental phenomenon. If the thyroid is overactive, and this is most usually associated with a nodular type of goiter, there may be an increase in heart rate and metabolism, and the heart may increase in size and in rare instances congestive heart failure may take place. However, this is most unusual, and probably is unrelated The so-called acromegalic heart is probably the result of a number of factors which are aggravated by the acrome-

tite. In fact, the acromegalic generally has a greater requirement for food and eats considerably more than the normal person, even though there is no associated hyperthyroidism.

DIABETES

Diabetes may be the first complication to be detected. The so-called diabetogenic hormone of the anterior pituitary is now generally considered to be the growth hormone. Growth hormone has some inhibitory action on the peripheral utilization of sugar. As a result of this, the islet cells of the pancreas become overactive in an attempt to compensate for this failure of glucose utilization. Far more insulin is poured out until such a time that the pancreas itself becomes exhausted and is unable to supply insulin, and clinical diabetes results. Diabetes in the growing pituitary giant before the age of puberty has not been reported, perhaps because the demands for growth allow for utilization of carbohydrate needed in the synthesis of protein tissue.

EFFECTS ON BONE

The action of growth hormone is not upon any of the endocrine glands themselves other than one of increasing the size of a gland without increasing its secretion. Growth hormone acts directly on the epiphyses and long bones and is a method of assaying the potency of growth

made. One can expect to find very little that is abnormal in the blood other than the usual elevation of the serum inorganic phosphorus. During growth in the pituitary giant, the inorganic phosphorus as a rule is higher than the usual elevation of childhood alone, and it continues well on into adolescence. These data should be sufficient to establish the diagnosis of gigantism or acromegaly with the aforementioned abnormalities taken into consideration. A basal metabolism is advisable if there is a suggestion of hyperthyroidism and also a glucose tolerance curve is advisable to detect any diabetic tendency if there is not frank diabetes.

TREATMENT

If considerable hyperthyroidism exists, it will respond to antithyroid drugs in the usual doses required for hyperthyroidism, although it takes a considerably longer time to bring the metabolism down to normal. The question of use of radioactive iodine must be considered also in the treatment of hyperthyroidism in acromegaly. In the absence of visual disturbance or headache, hyperthyroidism when present should demand the first attention in treatment since it is apt to be the most annoying feature. Subtotal thyroidectomy also can be carried out, but hyperthyroidism may recur unless the pituitary has been adequately treated. Even in such a case, hyperthyroidism may recur when seemingly adequate x-ray therapy has been given to the pituitary.

galic process. In the author's experience, heart disease is uncommon except in the older age group.

DIAGNOSIS

As mentioned before, elevation of the inorganic phosphorus is one of the best methods for the immediate determination of the activity of the acromegalic process. Roentgenograms of the sella almost invariably show enlargement, but there are rare instances where there is no apparent enlargement of the sella, the eosinophilic adenoma being overactive but not of sufficient size to cause this change in the contour of the sella. It is distinctly possible in some cases, although these would be extremely rare, that the anterior hypophysis may be located outside of the sella and a pituitary adenoma arise in these aberrant sites. In other instances the eosinophilic adenoma may extend through the capsule before causing any great enlargement of the sella and grow laterally or forward beyond the sella turcica, thus not causing any great enlargement. When a patient with suspected gigantism of pituitary origin or acromegaly presents himself, the usual routine in investigating these cases is, first, roentgenogram of the skull and sella turcica; secondly, a visual field examination, although one should not expect such changes in early gigantism and rarely in early cases of acromegaly.

A urinalysis, of course, should also be done, especially for sugar and, if possible, a blood sugar determination

performed in a given case. However, eosinophilic adenomas are more prone to recur than other types of pituitary tumor and periodic examinations should be made on these patients at least twice a year after treatment.

Estrogens are potent inhibitors of the pituitary and in some cases mild acromegaly and perhaps in more severe acromegaly without great enlargement of the sella, growth hormone activity may be suppressed by the administration of this hormone. Stilbestrol in adequate dosage of 1 to 1 5 mg. per day will decrease the serum inorganic phosphorus in either male or female. In general, its use should be reserved for active cases in which x-ray therapy for one reason or another cannot be given.

Sometimes before x-ray treatment can be given, or during the course of x-ray therapy, or even after, hemorrhage may occur into the tumor causing rapid deterioration of vision, at which time surgery is advisable to save or restore vision

RESULTS OF TREATMENT

When amenorrhea exists, in patients with active acromegaly, x-ray therapy or surgical removal of the major portion of the tumor may be followed by restoration of normal menstrual function.

Diabetes may decrease in severity after x-ray therapy or surgery, but often it has become fixed and insulin will be required thereafter, as in any ordinary case of diabetes mellitus.

It was mentioned in a few paragraphs above that hem-

In one of the author's cases the turnover of tracer doses of radioactive iodine was so rapid that no uptake measurements were possible, but radioactive iodine treatment was applied with satisfactory results.

The immediate treatment, by and large, depends on the most pressing problem. Headache, usually bitemporal, but by no means confined to these areas, along with visual change, certainly demands x-ray therapy to the pituitary. Diabetes may be severe and require immediate attention because patients with diabetes in acromegaly may also go into diabetic coma. The diabetes is treated as any ordinary type of diabetes mellitus, but in some instances is thought to require more insulin than would be expected.

One should caution the patient with acromegaly against overeating, even if no diabetic tendency has been found by fasting blood sugars or glycosuria. Glucose tolerance curves should be a routine study on first examination or at least a blood sugar taken two hours after a good meal. This advice applies to the period before treatment as well as after treatment. The sudden appearance of diabetes may thus be averted. It may be surprising to see diabetes develop after apparently successful treatment, but there may be irreversible changes in the pancreatic islands which cannot withstand excessive food intake.

With present methods of x-ray therapy in doses of 4000 to 5000 tumor roentgen units by the rotational method, it is unlikely that surgery will ever have to be

to the interval history and physical examination. Skull roentgenograms perhaps need not be taken oftener than once every one or two years unless there is a special reason to do so. It is to be remembered that the activity of the pituitary adenoma may continue without change in the size of the sella turcica. Levels of inorganic serum phosphorus below 4 mg. probably indicate subsidence of growth hormone excess, but values from 4 to 4.5 mg. may indicate a low grade activity. In such cases comparison should be made of the size of the frontal sinuses and the length of the mandible in films taken several years apart. Any increase in the size of these structures indicates a continuation of the acromegalic process despite no change in the size of the sella and minor elevation of the serum phosphorus.

FUGITIVE ACROMEGALY

The term "fugitive acromegaly," first coined by Dr. Harvey Cushing, is usually the result of a mixed type of tumor of the pituitary gland. By mixed type is meant one with eosinophilic elements as well as chromophobic elements. Initially, the overactivity of the eosinophilic elements causes some acromegalic changes, but this overactivity subsides and the patient winds up with the clinical picture of mild acromegalic changes but with evidence of hypopituitarism such as mild anemia, loss of some sexual hair, loss of sexual drive and low metabolism, often hypotension.

orrhage may take place into an adenoma and if surgery is necessary for purposes of saving vision or, if it is not, the hemorrhage may cause considerable destruction of the functioning part of the pituitary gland, followed by hypopituitarism. This is spoken of as pituitary apoplexy. Very few develop symptoms of hypopituitarism afterwards, although this is always to be looked for and can be adequately treated (see Adult Hypopituitarism).

Relief from headaches with x-ray treatment is variable. In the first place, a great number of people in the general population have headaches of various types, including migraine, and these, too, may occur in the acromegalic. It is therefore not always possible to predict relief of headache since it is not possible to determine whether it is due to the enlargement of the tumor itself, or to some other cause. The author has been impressed with the possibility that in acromegaly there may be head pain not due to pressure but perhaps due to growth hormone. There is no proof of this; it is merely surmised in instances where there is no sign of increasing size of the pituitary tumor. Such headache may persist in some instances where the sella becomes smaller after x-ray therapy. X-ray therapy to pituitary tumors may cause a decrease in the size of the sella turcica in acromegaly or gigantism, but it has not been observed in x-ray therapy for other types of pituitary tumors such as chromophobe adenoma or craniopharyngioma.

Follow-up examination should consist of a fasting inorganic phosphorus, visual field examination in addition

orrhage and shock occurring at that time. As stated before, craniopharyngioma may cause hypopituitarism on the average around the age of 16 or 17 but may manifest itself earlier or later in life.

SELECTIVE PITUITARY DEFICIENCY

What are the signs and symptoms which might lead one to suspect hypopituitarism? Let us first consider the selective deficiencies. Eunuchoidism in the male or female may be due to a selective deficiency of gonadotropic hormones with very little or no evidence of other anterior pituitary hormone deficiencies. These persons grow at a normal rate but lack only gonadotropic stimulation. In contrast to this, other cases of eunuchoidism may be due to primary testicular deficiency but the clinical picture is as a rule pretty much the same. The diagnosis of selective gonadotropic deficiency of the anterior pituitary can be established by the use of chorionic gonadotropin. If the condition is due to gonadotropic deficiency, the testes in the male will respond to chorionic gonadotropin, they will enlarge in size and secondary sexual characteristics will eventually develop. This can be used as a clinical test but for practical treatment eunuchoid males should receive testosterone orally, intramuscularly, or by pellet implantation

In the author's experience, several eunuchoid persons and one panhypopituitary case have become fertile by the use of testosterone or by the use of chorionic gonado-

X-ray therapy should be given to these patients if there is evidence of changes in visual acuity or visual field defects, but a resumption of normal pituitary activity is not to be expected in this type, in contrast to the resumption of normal menstruation which so frequently follows x-ray treatment of acromegalic women.

In males who have developed hypopituitarism, testosterone of long-acting type may restore normal sexual drive and cause regrowth of body and sexual hair and in general a feeling of well-being, with increased stamina and less fatigue. This may also be given to females, but cortisone in 25 mg. doses may counteract the lassitude, and in some cases the anemia, but does not cause a resumption of menstruation, or libido in male or female.

ADULT HYPOPITUITARISM

Adult hypopituitarism can be classified under selective deficiencies of various anterior pituitary hormones, or panhypopituitarism, in which all of the anterior pituitary hormones appear to be deficient.

In clinical practice the commonest cause of hypopituitarism involving several of the anterior pituitary hormones is a chromophobe tumor of the pituitary gland. Destruction of the anterior pituitary gland (Simmonds' disease) may also result from septic processes, encephalitis, and sometimes without known cause. Infarction of the pituitary arteries, known as Sheehan's disease, which follows childbirth, is due to excessive uterine hem-

pituitary is present or absent. (Treatment of amenorrhea associated with normal secondary sexual characteristics will be discussed under the chapter on Ovaries.)

The mechanism of anovulation may be due to hypothalamic interference with the normal elaboration of pituitary luteinizing hormone. Marked psychological trauma may inhibit ovulation and probably is responsible for more of the temporary amenorrheas in girls with normal secondary sexual development than anything else. In some cases, enlargement of the sella turcica may be found, suggesting some interference with pituitary function, yet not sufficient to prevent normal stimulation of the ovaries and hence estrogen production.

Amenorrhea, therefore, of six months' duration or longer should always make one suspect that the pituitary is at fault and routine x-rays of the sella turcica should be taken. In the histories of women with pituitary chromophobe adenomas, one frequently finds that amenorrhea has been the first symptom for which many treatments have been carried out previous to the development of other signs and symptoms indicative of a pituitary tumor.

Headache

With amenorrhea in cases of pituitary insufficiency there is loss of libido These symptoms may precede the local effects of tumor expansion by months or years, depending on the rate of the growth of the chromophobe tumor. In many instances the first evidence of a pituitary tumor

tropin and testosterone combined. It was difficult to conclude in the eunuchoid males whether they were suffering from extremely late puberty or whether the medication was instrumental in bringing about normal development. The testes enlarged under this therapy, spermatogenesis developed and full secondary sexual characteristics followed.

Eunuchoidism in the female, whether due to gonadotropic deficiency or ovarian deficiency, cannot be differentiated as easily as in the male because of the lack of effect of chorionic gonadotropin. If urinary hormone assays are available, an ovarian deficiency resulting in eunuchoidism will show excessive follicular stimulating hormone in the urine typical of the menopausal patient. (Eunuchoidism and eunuchism in general will be discussed under Diseases of the Testes and Ovaries.)

Amenorrhea

There is another theoretical pituitary insufficiency occurring in some women who have apparently developed normally as regards secondary sexual characteristics, yet who do not menstruate. Basal temperature charts show failure of ovulation. Vaginal smears, which will be described later, may show full estrinization of the vaginal epithelial cells. These cases can therefore be ascribed to failure of ovulation due to deficiency of the anterior pituitary hormone which stimulates ovulation. This is purely theoretical since there are no good tests which can determine whether or not luteinizing hormone of the anterior

Sheehan's Disease

Hypopituitarism associated with infarction of pituitary arteries can be suspected in women who become amenorrheic after childbirth along with fatigability, anemia, loss of sexual hair, hypotension, and low metabolism. In these cases, of course, there are no signs of intracranial pressure, such as headache or visual disturbance.

Careful inspection of the entire body is important and is often not done in women who appear anemic. The finding of diminished or absent sexual hair (pubic and axillary) should at once direct one's attention to the possibility of hypopituitarism and a careful interrogation regarding events which occurred at childbirth.

Then there are those who develop hypopituitarism from craniopharyngioma and in these cases, too, it is likely, but not always, that the headache or visual disturbances are the main symptoms which point to the real diagnosis.

Visual Change

In view of what has been said, it would seem likely that before visual field changes occur there must be considerable hypopituitarism present This actually is not the case and the probable explanation is that the chromophobe adenoma has broken through the capsule of the diaphragm of the sella and grown outward, thus releasing pressure upon the normal pituitary cells remaining, permitting normal glandular function. We have seen patients with normal menstruation who have gone through

is not in glandular complications but headache, which is not characteristic except that it is likely to be persistent rather than periodic. Eventually there may be change in vision. During this period of growth of the chromophobe pituitary adenoma, there may be lassitude and pallor. It is surprising, however, that headache or only some loss of vision may be the first symptom without other associated complaints.

OTHER SYMPTOMS OF HYPOPITUITARISM

When all anterior pituitary function is suppressed, then a fairly characteristic picture ensues. There is lassitude, definite pallor, beginning loss of sexual hair, hypotension and low basal metabolic rate. Occasionally, however, the patient may present the classical picture of myxedema. If all anterior pituitary function is decreased, the clinical picture of myxedema does not seem to occur. It has to be admitted, however, that some patients with chromophobe tumors may share all the clinical findings of myxedema and it is for this reason that all patients with spontaneous myxedema should have x-rays of the sella turcica. The reason for the predominant deficiency of thyrotropic hormone in these cases is obscure, but it may be postulated that there existed a low thyroid reserve which preceded the onset of hypopituitarism. (See pages 149, 150 for ACTH Tests.)

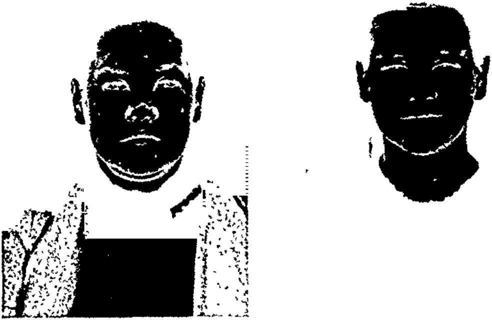


Fig. 4. Myxedema before and three months after administration of desiccated thyroid.

pregnancy in spite of the fact that they have a large sella with gross visual field defects.

In a survey of over 180 of our patients with chromophobe pituitary adenoma, one of the most striking features of the history was that many had been treated for weakness, fatigue, anemia and amenorrhea long before a chromophobe tumor was suspected. In view of the lack of evidence of hypopituitarism in some cases occurring with chromophobe tumor, it is therefore important that x-ray of the skull and sella turcica be taken on all females who have had amenorrhea for more than six months, unless there is some other obvious disturbance such as extreme malnutrition and even in this instance x-rays are worth while. Women with chromophobe tumors as a rule are fairly well nourished and the average weight distribution is about the same as for the normal female.

What procedure should be carried out in case a woman is found to have a large sella turcica without headache or visual field defects and in whom there is amenorrhea? From experience it has been definitely shown that x-ray therapy of an enlarged sella without visual field defects or headaches is not followed by appearance of menstruation unless the enlargement is due to an eosinophilic tumor associated with acromegaly. Treatment, therefore, of the presumed pituitary adenoma should be reserved for those who have visual defects or headache and in whom there is reason to believe that there is actual pressure.

Not infrequently an enlarged sella is found in women who are of highly neurotic dispositions, whose headaches

are usually due to nervous tension and in whom there is no evidence of glandular deficiency or visual defects. These patients should be followed, but all reference to possible pituitary tumor in the head should be avoided since this is a frightening situation to the average patient and will only increase her neurosis. The situation could be put in a milder way by saying that there may be some enlargement of the pituitary gland, but reference to a tumor is too alarming unless there is adequate evidence as shown by follow-up that there is increasing size of the sella or other features which point to pressure.

Anorexia Nervosa

Anorexia nervosa is usually followed by amenorrhea, low metabolism, and considerable loss of weight. As stated previously, this may be due to a secondary anterior pituitary deficiency as the result of starvation. The diagnosis is usually readily made, first by the lack of evidence of enlargement of the sella turcica* and secondly by the fact that in most instances anorexia nervosa occurs in the young, unmarried female and there is no history of pregnancy or shock. There may also be no history of cerebral disturbance which would suggest encephalitis or other infection In spite of the marked malnourishment, the patients with anorexia nervosa are usually active and are not particularly concerned about their condition.

* Craniopharyngioma may exist without enlargement of the sella turcica, or suprasellar calcification, displacement of the pineal should be looked for.

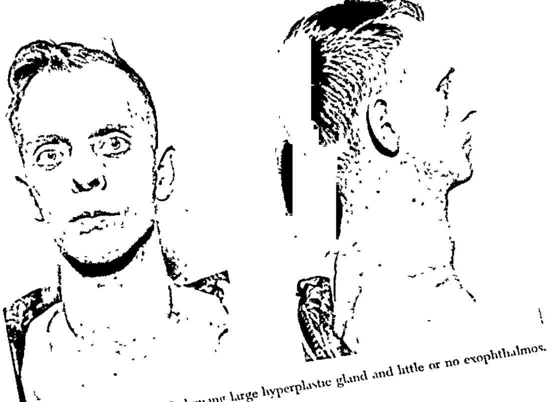


Fig 5 Graves' disease in a man of 29 showing large hyperplastic gland and little or no exophthalmos. Note stare, due largely to lid retraction

true in our experience. If the patient is in the hospital, forced feeding may be advisable and intravenous feeding if the patient does not cooperate. This may start the patient on the road to recovery. Only in cases where a serious psychiatric problem exists is the prognosis not too good. The condition rarely exists in men and the only instance we have seen was greatly helped by a lobotomy after many attempts to induce the patient to eat.

Hormonal therapy is ill advised in the author's opinion. It is true that estrogens can be administered along with progesterone and menstrual bleeding occur, but it is far better to get the patient back on a normal nutritional basis following which normal menstruation should occur. Great hopes were held out for the treatment of anorexia nervosa by the use of cortisone and ACTH but they have not proven of value.

TREATMENT OF CHROMOPHOBE TUMOR

The first principle of treatment in chromophobe pituitary tumor is that of relief of pressure and restoration of normal visual acuity and normal visual fields. X-ray therapy is to be preferred and is successful in the majority of cases. However, there are instances where vision is deteriorated to the extent of almost complete blindness and x-ray therapy should not be used in such cases; rather, surgery is the treatment of choice. Even surgery, however, may not remedy the loss of vision but may offer a better chance than x-ray because the edema following x-ray

The degree of glandular deficiency in anorexia nervosa may develop to the point where there is a decrease in urinary hormones and absence or decrease in glycogen in the vaginal smear. However, it rarely progresses to the extent of loss of sexual hair which certainly would be greatly diminished if the case was one of significant primary anterior pituitary deficiency.

A patient with hypopituitarism does not have the extreme anorexia a patient with extreme malnutrition has, unless there is considerable increase in intracranial pressure. There is another type of anorexia nervosa which presents the same clinical picture except that the patient eats very well. In such cases one should always suspect surreptitious vomiting of food after eating and it may take considerable detective work to prove this. The author has employed several methods of proving that food is vomited. In the first place, a few barium capsules can be administered with the meal and then x-ray pictures taken an hour or two later Naturally if the patient has vomited her food, the capsule of barium cannot be seen. Another method is by hospitalization, careful account taken of the food eaten and the protein composition of it. A twenty-four hour urine specimen taken over several days for nitrogen excretion should demonstrate that the food swallowed has not been ingested

The treatment of anorexia nervosa is difficult. Some psychiatrists state that there is little to be accomplished with psychiatric therapy and that in most instances these young girls overcome it themselves. This has usually been

hair but testosterone will, and can be used for this purpose in male or female if for no other.

Administration of desiccated thyroid is as a rule disappointing unless the patient shows definite evidence of clinical myxedema, namely, dry skin, lack of perspiration, puffiness about the eyes, or some falling of head hair in addition to sexual hair.

The anemia of hypopituitarism is not reactive to iron, liver, or any known form of anti-anemic therapy, but does respond to testosterone in some instances and to cortisone or ACTH in others. However, these preparations are not always effective and patients must therefore go along with mild secondary anemia, symptoms of which are not particularly felt by the patient once cortisone has been used. Ideally, ACTH gel is superior in view of the fact that it keeps the adrenal cortices active. Cortisone theoretically further depresses the output of adrenal cortex; it was thought originally to be dangerous if by chance the patient discontinued cortisone. Actually discontinuance of cortisone in quite a number of patients has occurred without any severe reaction, the reason probably being that the whole metabolic level of the body is lowered so that not too much adrenocortical hormone is necessary to sustain life. This is in contrast to Addison's disease in which the omission of cortisone might be followed by severe adrenal insufficiency because other hormones of the body are being secreted in normal amounts, and the general metabolic rate is at a higher level and thus the need for cortisone is greater.

treatment may further decrease vision. The same danger of course exists in the surgical approach. Previously it was thought that chromophobe tumors were not sensitive to x-ray treatment but it is now recommended as the treatment of choice in the average case. The same dosage is given in acromegaly. No improvement in glandular deficiency is to be expected following either x-ray treatment or surgery for chromophobe pituitary tumor. If it occurs, it is most fortuitous.

TREATMENT OF HYPOPITUITARISM

The treatment of hypopituitarism has been greatly simplified by the use of cortisone. ACTH gel can be used, which will increase adrenocortical secretion, but for practical purposes cortisone is much easier to take and a surprisingly small amount will restore these individuals to fairly normal health. The average dose does not exceed 25 mg. and in fact some patients get along very well with 12.5 mg. daily.

Before the advent of cortisone and ACTH, testosterone was used by the author in the form of pellet implantation or long acting depo-testosterone in both male and female. In addition, desoxycorticosterone acetate was used because of secondary adrenal insufficiency. Neither of these now need be used except possibly testosterone in the male in an attempt to restore normal sexual function which in an occasional case may be accomplished. Cortisone itself will not cause regrowth of pubic and axillary

PREPARATION FOR SURGERY

Patients with chromophobe tumor coming to operation should be adequately prepared for surgery and this can be accomplished by the administration of 100 mg. of cortisone daily before and after operation. For surgery, however, it might be well worth while giving ACTH gel before surgery or using 20 units of corticotropin in slow, intravenous infusions over a period of six to eight hours for several days before surgery. ACTH gel, 100 mg. per day, is also used. Cortisone and corticotropin may be given simultaneously.

RESULTS

The results in the treatment of chromophobe pituitary tumor, either by surgery, x-ray therapy, or both, as summarized in 95 cases with visual disturbance, show that there was improvement of vision in 73 cases, no change in 11 cases and a worsening in 11 cases Complete restoration of vision was accomplished in about 25 per cent and a good return in an additional 50 per cent. Many of these patients would not have had deterioration of vision had the condition been recognized earlier in the course of the disease Eighty-nine of the total group of 144 showed evidence of hormonal deficiency. None were unequivocably improved in this regard by x-rays, surgery, or both

It is wise, however, to advise patients before taking cortisone to double the dose of cortisone if there is an acute infection, if there has been an accident, or need for surgical intervention. The dose may not only be doubled, but perhaps quadrupled if the stress is severe. Some patients with hypopituitarism have noted general weakness *of a serious degree during acute infections* and have automatically increased their dosage of cortisone, but this is not so likely to happen as in a patient with Addison's disease who is on cortisone.

In other diseases of the adrenal glands, the use of the water test will be discussed. The water test is positive in hypopituitarism, but may be restored to normal by the use of cortisone. Thus the water test may not be a specific indicator of salt metabolic hormone. As a matter of fact, *patients with hypopituitarism do not suffer* the consequences of sodium loss as do patients in Addison's disease.

A probable answer to this is the fact that the zone of the adrenal cortex which regulates salt metabolism may be independent of the anterior pituitary, thus explaining why, in part at least, serious consequences of salt loss are not noted in *hypopituitarism*

Patients with hypopituitarism may also have hypoglycemic episodes, although these are quite rare and much less frequent than in Addison's disease Cortisone regularly taken, because of its hyperglycemic effect, will prevent these in both hypopituitarism and in Addison's disease.

It has often been conjectured that the removal of the anterior and posterior pituitary together is not followed by diabetes insipidus. It has been concluded, therefore, that the anterior pituitary secretes a hormone which antagonizes the effect of the secretion from the posterior pituitary. Thus, the posterior pituitary is antidiuretic and the anterior pituitary is diuretic. In the past few years hypophysectomy has been carried out for malignant disease and this theory has been supported in that those patients in whom diabetes insipidus developed after this procedure were found on postmortem examination to show remaining anterior pituitary tissue.

Other conditions are thought necessary for the development of diabetes insipidus, namely, that the thyroid gland function is normal, that there is no serious disorder of the kidneys, and that there is injury of other nerve centers in and about the hypothalamus.

Diabetes insipidus may appear without a history of previous illness or without any other discoverable cause when once present. As stated previously, it may follow operations upon the brain, especially in the region of the pituitary gland.

It may be associated with tumors or cysts of the pituitary, hypothalamus, mid brain or third ventricle. It may follow infections, such as encephalitis or other infectious disease. It may occur as a result of trauma with fracture or in the Laurence-Moon-Biedl syndrome.

Occasionally, it is associated with lipoid granulomatosis, also known as Hand-Schuller-Christian syndrome. This

DIABETES INSIPIDUS

Diabetes insipidus may vary greatly in the amount of water which the patients ingest and excrete. When the condition is a result of surgery in or around the pituitary gland, it may gradually improve; thus we know that the condition can exist with the excretion of only 4 or 5 quarts a day. Diabetes insipidus responds to pitressin, whereas a normal person drinking and excreting this much would have no decrease in water intake and output. On the other hand, the volume of urine may be greater than 20 liters. The urine excreted is practically colorless and the specific gravity is dependent on the amount of urine passed. It is unusual to find a specific gravity in diabetes insipidus over 1.005, but in milder cases it may reach 1.010.

The disease may be persistent or relapses or remissions may occur without known cause. The average age of the patient with diabetes insipidus is around 21; it frequently occurs before the age of 10 and rarely after the age of 50 or 60. Males predominate, the ratio being about 2 to 1.

The source of this curious disorder lies in the posterior lobe of the pituitary gland and it is caused by a decrease or absence of the posterior pituitary secretions, especially pitressin. Due to the absence of this hormone in the circulation the kidney tubules are unable to resorb water as they do normally. Pitressin, therefore, acts on the kidney tubules. The increased thirst is due to the excessive water loss.

legs, nausea and vomiting, often headache, faintness and tachycardia, sweating, possibly hypothermia, psychic disturbances and even collapse.

The symptoms on withdrawal are usually disagreeable enough to warrant a positive diagnosis of diabetes insipidus unless there is an associated and rather severe neurosis.

Special intravenous tests may be done by giving the patient salt. This may be taken orally. The patient omits his breakfast and is then given 0.25 gm. of sodium chloride per kilogram or in a 10 per cent solution. For the next five hours, the following tests are determined. Sodium chloride is determined in the serum in milligrams per 100 cc., and in the urine in milligrams per minute; the total urine excreted is recorded in cubic centimeters per minute.

Normally, the concentration of sodium chloride rises in the serum and in the urine and the output of urine per minute is essentially unchanged. In diabetes insipidus, however, the serum chloride concentration rises and the urine concentration remains very low Urinary output per minute is moderately increased.

A simpler test is as follows: only 1.5 gm. of sodium chloride is permitted for several days in the diet of the patient with diabetes insipidus. Nothing unusual happens to the normal individual. However, in diabetes insipidus, the urinary volume and chloride concentration are decreased.

A more elaborate test consists of inserting an indwell-

disease may not reveal itself until some time after the development of diabetes insipidus. There appears to be a familiar tendency to diabetes insipidus.

DIAGNOSIS

Not every patient who drinks and excretes a lot of water has diabetes insipidus. Diabetes mellitus may be the cause of these symptoms and this, of course, can be determined by the finding of glycosuria. In rare instances, however, diabetes insipidus and diabetes mellitus may be associated.

The most likely situation in which one might suspect diabetes insipidus is in functional polyuria or polydipsia. This is apt to occur in nervous females and great quantities of fluid may be imbibed. It is not unusual to find that such patients are taking pitressin or posterior pituitary extract. There is still another disorder occurring mostly in children and not due to posterior pituitary disease but caused by some intrinsic abnormality in the tubules of the kidneys themselves.

To distinguish between nervous polydipsia and diabetes insipidus, the first step is to attempt to limit the fluids of the patient for twenty-four to forty-eight hours. In spite of the patient's statement to the contrary, the nervous patient will be able to withstand fluid retention whereas the patient with diabetes insipidus will suffer great distress, especially if the disease is severe.

This distress consists of cramps in the abdomen and

If there is evidence of disease in and about the pituitary, x-ray therapy could be tried but I have not seen this to be more than temporarily effective.

Amidopyrine has often been used in the past and can be tried in milder cases.

The effects of overdosage of pitressin tannate include urinary suppression, water retention, gain in weight and then the generalized symptoms such as headaches, restlessness, drowsiness, fainting, weakness and pallor.

Diabetes insipidus is, as a rule, fairly easy to control. Patients feel that certain lots of pitressin tannate are not as effective as others and this has been proved to be true. Patients have stated that the solutions of pitressin tannate in oil which are slightly hazy appear to be more effective than those which are clear. Apparently, the method of standardization is difficult and, as I understand, those persons who put up pitressin tannate in oil are not too surprised at this variation.

The outlook is good for patients with diabetes insipidus unless it is associated with some advancing disease. Spontaneous remissions may occur, but not too frequently. Once the dosage of pitressin tannate has been established, the amount necessary to control the disease usually does not change. However, if diabetes insipidus follows some operative procedure, there may be a gradual tendency for improvement.

ing catheter and giving pitressin intravenously. In the normal individual the flow is decreased because of the intravenous injection of sodium chloride. In diabetes insipidus, however, there is continued diuresis even after the intravenous injection of salt but prompt decrease when pitressin is administered.

TREATMENT

The treatment of diabetes insipidus from a practical point of view is the administration of either powdered posterior pituitary gland or pitressin tannate in oil. Powdered posterior pituitary gland is given intranasally and is snuffed up from a small applicator two or three times a day as required to control symptoms. The only difficulty with this method of treatment is the local vasomotor rhinitis that may follow its use.

The injection of pitressin tannate in oil is the most satisfactory treatment. One cubic centimeter containing 5 pitressin units may relieve symptoms for from twenty-four to eighty-two hours. This also would have to be determined by trial and error. Smaller doses may be used.

Various other recommendations have been made for patients with diabetes insipidus. If a patient has an associated hyperthyroidism, the symptoms may subside after subtotal thyroidectomy. In fact, total ablation of the thyroid without hyperthyroidism has been reported to improve diabetes insipidus, but this certainly is a questionable procedure.

only cause of thyroid enlargement as there are certain substances which may interfere with the absorption of iodine or at least its incorporation into thyroid hormone. These are known as goitrogenic agents and the list of foods or other substances which are goitrogens has not been fully explored. Because of the goitrogenic effect of cabbage on rabbits, the pursuit of compounds of pure nature causing goiter was sought and hence the final discovery of compounds such as thiourea, thiouracil, and many others.

COLLOID AND ENDEMIC GOITER

Endemic goiter regions are well known and generally are centered chiefly around mountainous areas. Some other goitrogenic conditions which have been suggested are, in addition to deficiency of iodine, certain vitamin deficiencies, excess of fat or fatty foods, lime, or possibly bran, cabbage, nuts, maize, turnips and rutabagas. In addition to thiourea derivatives, such agents as cyanates, cyanides and other compounds are known to be goitrogenic. Certain epochs during life are thought to increase the appearance of simple goiter, namely, puberty, pregnancy, and menopause.

Simple goiter, or simple colloid goiter may occur at any time, but is most frequently seen in early childhood or early adult life. In goiter areas, of course, children may be born with this type of goiter. In the early stages of colloid goiter there is a simple, symmetrical, spongy enlargement

CHAPTER III

DISEASES OF THE THYROID GLAND

In contrast to the pituitary gland, the thyroid gland apparently has only one hormone the exact nature of which has not been definitely identified. It is, of course, an iodine bearing hormone and there are several iodine bearing compounds which have the same effect upon the human body in raising the metabolism such as thyroxin, and more recently triiodothyronin. Because of the necessity of having iodine incorporated into the thyroid hormone, the thyroid gland has a great avidity for circulating iodine in the body. Radioactive iodine administered by almost any route will quickly show up in the thyroid gland.

Inability of the thyroid to procure iodine results in various degrees of a decrease in thyroid hormone synthesis and is often accompanied by enlargement of the thyroid. This is one of the long recognized reasons for enlargement of the thyroid in goiter belts, but this is not the

malignancy developing in a multiple nodular goiter is certainly not a great hazard and it is doubtful if it exceeds 1 per cent.

The discrete tumor of the thyroid may be malignant even in childhood. In fact, statistics seem to indicate that a discrete nodule before the age of fifteen shows a higher percentage of malignant change than one thereafter.

The greatest difficulty lies in recognizing a discrete tumor of the thyroid. To experienced clinicians a discrete nodule may turn out at surgery to be only a nodule in a multiple nodular goiter. However, it is better to remove what appears to be a single nodule and find it part of a multiple nodular goiter than to do nothing about it.

Some malignancies of the thyroid progress very rapidly, particularly the small cell or giant cell type of carcinoma. Even with removal the eventual outcome is at best no more than 50 per cent survival in a five year period. For the less malignant types, the five year survival rates are above 75 per cent. These include the fetal adenoma with invasion, the papillary adenocystoma and the papillary adenocarcinoma.

Malignancy of the thyroid may be encountered in routine subtotal thyroidectomy for hyperthyroidism or, as noted above, in multiple nodular goiter. These might be considered carcinomas *in situ* and may remain latent for years. In fact, experience has shown that there has been a known tumor in the thyroid prior to the diagnosis of cancer of the thyroid as long as ten years before and on the average a lump has been noted at least four years before

without nodules. As the goiter increases in size and because of certain as yet undetermined factors, nodules may form which are essentially aggregations of distended follicles followed by scar tissue formation and this may proceed to the extremely large multiple colloid nodular type of goiter.

As a rule there is no gross disturbance of thyroid function with simple colloid or endemic goiter, and no treatment is imperative unless it is unsightly or unless there is encroachment upon the trachea. As time goes on and because of the traction occasioned by swallowing, the goiter may descend into the superior strait of the thorax and become wedged therein or may become intrathoracic.

The administration of iodine is seldom accompanied by a reduction in the size of the goiter. The administration of desiccated thyroid in doses of not over 1 grain a day for the average young adult or one-fourth to one-half grain in children is said to be followed by a decrease in size of simple goiter. This is most likely to occur if there is an associated thyroid deficiency.

MALIGNANCY OF THE THYROID

Multiple nodular goiter, the usual outcome of simple colloid goiter is not often the seat of malignant degeneration, although it cannot be denied that it exists. Whether it arises in this type of goiter or whether it is a coincidental affair has yet to be determined, but the incidence of

malignancy developing in a multiple nodular goiter is certainly not a great hazard and it is doubtful if it exceeds 1 per cent.

The discrete tumor of the thyroid may be malignant even in childhood. In fact, statistics seem to indicate that a discrete nodule before the age of fifteen shows a higher percentage of malignant change than one thereafter.

The greatest difficulty lies in recognizing a discrete tumor of the thyroid. To experienced clinicians a discrete nodule may turn out at surgery to be only a nodule in a multiple nodular goiter. However, it is better to remove what appears to be a single nodule and find it part of a multiple nodular goiter than to do nothing about it.

Some malignancies of the thyroid progress very rapidly, particularly the small cell or giant cell type of carcinoma. Even with removal the eventual outcome is at best no more than 50 per cent survival in a five year period For the less malignant types, the five year survival rates are above 75 per cent. These include the fetal adenoma with invasion, the papillary adenocystoma and the papillary adenocarcinoma.

Malignancy of the thyroid may be encountered in routine subtotal thyroidectomy for hyperthyroidism or, as noted above, in multiple nodular goiter. These might be considered carcinomas *in situ* and may remain latent for years. In fact, experience has shown that there has been a known tumor in the thyroid prior to the diagnosis of cancer of the thyroid as long as ten years before and on the average a lump has been noted at least four years before

the final diagnosis was made. Metastases to cervical glands have been noted for many months in some instances before it was realized that it might be due to malignancy of the thyroid.

Obvious advanced clinical cancer of the thyroid is fairly easily recognized because of the hardness and the fixation, in which case the prognosis is usually none too good.

DIFFERENTIAL DIAGNOSIS OF TUMORS OF THE NECK

Tumors of the thyroid are to be distinguished from thyroglossal cysts which usually occur in the midline and which are attached to the hyoid bone. Often fistulas may be present. It is also to be differentiated from branchial cysts or sinuses which occur laterally, usually soft and fluctuant and may become abscessed. These grow rather slowly and have a history of recurrence, swelling and soreness. Laryngocele is a rare tumor in the neck. It is opposite the level of the larynx, unilateral and may enlarge on swallowing or holding the breath. Primary carcinoma of the glands of the neck, Hodgkin's disease, inflammatory tuberculous glands, parathyroid adenomas, carotid body tumors are all to be considered in the differential diagnosis.

MECHANICAL SIGNS AND SYMPTOMS OF GOITER

Enlargement of the thyroid even when impinged in the superior strait or intrathoracically, rarely causes difficulty in swallowing. The most common cause of difficult swallowing is globus hystericus and this may be present in patients with enlargement of the thyroid. Difficulty in swallowing may also be due to esophagitis which when associated with goiter and anemia is termed the Plummer-Vinson syndrome.

If the goiter is due to cancer and is invasive, then it may cause occasional difficulty in swallowing. On the other hand, difficulty in breathing may be due to pressure upon the trachea. It is to be differentiated from the nervous type of sighing or difficulty in breathing in patients with goiter who do not have encroachment upon the trachea.

When pressure upon the trachea is sufficient there is usually stridor, and if this is not manifest it can be revealed by having the patient turn his head to one side or the other, forward or backward, which will compress the trachea over the enlarged thyroid and cause further narrowing of the trachea and stridor. Sudden dyspnea with stridor in goiter may occur with hemorrhage into an adenoma or adenomatous goiter.

When the trachea is laterally displaced it can be readily detected by examining Adam's apple. However

retrotracheal goiter may not displace the trachea from one side to the other. Special x-rays of the trachea, using the Bucky diaphragm are valuable in detecting deviation or compression of the trachea either above the sternum or in the mediastinum.

Intrathoracic goiter may be associated with distended cervical veins, with enlargement of the veins of the abdomen, and with some edema and swelling of the face. It is to be differentiated chiefly from intrathoracic tumors, such as Hodgkin's disease, or in rare instances, aneurysm. In several instances of intrathoracic goiter which were thought certainly to be Hodgkin's disease and in which x-ray therapy caused no shrinkage, exploration revealed intrathoracic goiter but, by and large this mistake rarely occurs.

THYROIDITIS

Inflammatory conditions can give rise to enlargement of the thyroid such as tuberculosis, actinomycosis, or amyloidosis. Acute suppurative thyroiditis may occur with abscess formation. Then there is the acute nonsuppurative type of thyroiditis which is rather acute and may follow an upper respiratory infection. It is often associated with pain on swallowing, tenderness over the thyroid without elevation of the white count or sometimes without fever. General systemic symptoms may arise as in any infection. These usually subside in time; treatment has been recommended, such as thiouracil, cortisone and

antibiotics. Perhaps cortisone is the most satisfactory; if it does not quiet infection, at least it gives symptomatic relief. X-ray therapy has been effective in our hands.

There are several nonspecific chronic types of thyroiditis. One is thought to be associated with spillage of colloid, causing inflammatory reaction. Two of the best known types are Riedel's struma and Hashimoto's struma. Riedel's struma has also been called the woody thyroiditis. It is hard, sometimes unilateral and may be adherent to the trachea. The pathology is one of dense fibrous connective tissue. Hashimoto's struma, on the other hand, is characterized histologically by marked lymphocytic infiltration, often called struma lymphomatosa. It occurs in middle age or later life as in Riedel's struma, rarely in children; it predominates in the female, whereas in Riedel's struma, males and females are about equally affected.

The gland is usually bilaterally enlarged in Hashimoto's struma. Early in the disease it is likely to be smooth, but usually it is somewhat nodular. It is hard but not stony hard as in Riedel's struma. It is often considered clinically to be a nodular goiter. The diagnosis in either case must be made by biopsy or at operation. With thyroiditis there may or may not be thyroid deficiency or myxedema.

The chief point of concern here is differentiation from cancer of the thyroid. This is particularly true in Riedel's struma. Therefore, operation or biopsy should be performed.

The accuracy of clinical diagnosis of the different types of thyroiditis or, in fact, a good many types of enlargement of the thyroid leaves much to be desired.

Hashimoto's struma will respond to x-ray therapy and in fact has more recently been reported to respond to treatment with desiccated thyroid, on the average of 2 or 3 grains a day, according to the patient's tolerance. It may also decrease in size with the use of cortisone, since cortisone or ACTH is lympholytic in its effect.

It was stated earlier that in multiple colloid adenomatous goiter the size of the goiter may decrease on administering thyroid, especially if there is associated thyroid deficiency. It is probable that some of these cases were instances of Hashimoto's struma and not a true multiple colloid adenomatous goiter. It is, therefore, advisable to be fairly certain of what the disease in the thyroid is before attempting treatment.

The fibrous tissue of Riedel's struma may contract so that there is considerable anterior pressure on the trachea, and excision of the isthmus of the thyroid and removal of the struma may be necessary for comfort and also, as stated before, to be sure that carcinoma of the thyroid is not present.

Even though thyroid deficiency is not present at the time of operation and if operation is carried out, the chances of thyroid deficiency are increased by a generous removal of thyroid tissue.

CRETINISM

The exact definition of cretinism is nowhere to be found. The author in attempting to define cretinism finally concluded that all instances of thyroid deficiency before epiphysial closure, or the normal time of epiphysial closure, could be called cretinism. This includes such terms as endemic cretinism, congenital athyreosis, thyroaplasia, sporadic cretinism and infantile and childhood myxedema.

Thyroid deficiency conceivably may begin intra-uterine but it is not known definitely whether the fetus requires much thyroid hormone because of the low level of metabolic activity. Certainly newborn infants are rarely recognized as having cretinism unless attention is called to this possibility by the presence of a large goiter. In any event the physical signs of cretinism apparently do not begin to appear until about 3 months or later. X-rays of the hands and wrists of cretins recognized at about the age of six months show the bone age to be below that usually considered normal at the time of birth, indicating that the thyroid deficiency may have begun before delivery.

As mentioned previously, the cretin of infancy may not attract attention because of the fact that the child does not cry, sleeps a good part of the time, and is generally considered well behaved. It is not until the difficulty in feeding the child or the usual constipation shows up that something abnormal is considered possible

Slowly there appears the dull, lifeless expression, puffiness about the eyes, thick tongue, which may in infancy interfere with swallowing, pot belly, and sometimes umbilical hernia and failure to grow. Cretinism at this age is to be distinguished chiefly from mongolian idiocy as mentioned previously in the differential diagnosis of dwarfism.

Desiccated thyroid should be administered as soon as the condition is recognized. Delayed treatment may impair mental development at a later date. It is an established fact that most cretins do not attain a normal mental age, but a certain percentage apparently escape this brain damage.

Treatment of Cretins

Treatment in infancy should be according to the following schedule during the first year: 1/16 to 1/4 of a grain of desiccated thyroid should be administered daily; after that and up to three years, from one-fourth to one-half grain depending upon tolerance. From three to eighteen years, from one to one and one-half grains usually is sufficient. It is unusual to find a dose over 2 grains necessary even in adult myxedema.

Within a week or two after desiccated thyroid is administered, there is a remarkable change in the child and growth begins to occur at a normal rate. If goiter is present, there may be some decrease in size upon the administration of thyroid.

As a rule, the most striking changes occurring from

thyroid deficiency in childhood are slowing down in growth rate, the dry skin, the puffiness or bloat about the eyes and face, the dryness of the hair, lack of perspiration and mental sluggishness. Rarely excessive hair growth will accompany cretinism, the cause of which is obscure. In a few instances there may not be a fully developed clinical picture and the use of desiccated thyroid as a trial procedure is justifiable. Nowadays in large hospitals, where facilities are available, radioactive iodine uptake is found to be greatly decreased or almost absent in thyroid deficiency but metabolism tests are usually not worth while. Blood cholesterol is usually elevated.

The proof of thyroid deficiency usually follows treatment and if there is no decided change or response it can be certain that thyroid deficiency does not exist. As mentioned before, if thyroid deficiency has existed for several years, there will be a decided retardation of skeletal age, as shown by hand-wrist x-rays.

If thyroid deficiency occurs before pubescence, there is as a rule delayed menarche and sexual development, which appear fairly soon after desiccated thyroid is administered, if at the menarcheal age.

ADULT MYXEDEMA

Myxedema in adults occurs most frequently in women between the ages of 35 and 40, although no age is exempt, nor are males.

The complaints of a patient with myxedema are varied. The slowing down of mental processes makes the patient

with myxedema less conscious of his bodily discomforts in many instances. Often the patients are not even aware that they have myxedema and the condition is called to their attention or noticed by friends, particularly those who have not seen them for some time, as was mentioned in the recognition of acromegaly.

Sensitivity to cold and enjoyment of hot weather are fairly common. Dryness of the hair and inability to hold a permanent wave may be a chief complaint. Decrease in memory and mental sluggishness may be complained of. In some instances there is a decrease in hearing. Extreme fatigability or lack of energy is often present. Somnolence may be a prominent symptom. Constipation is often present.

Before menopause, the female with myxedma may have amenorrhea or may have menorrhagia, or there may be oligomenorrhea However, in rare instances, menstruation may not be particularly affected.

Diagnosis

The diagnosis is frequently overlooked because myxedema is a fairly rare disease but once the features of myxedema are pointed out it becomes obvious. Often these patients are thought to have nephritis because of the pasty, bloated appearance of the face. Some may actually show albumen and have hypertension Anemia varies but there is often a mild or secondary or hypochromic type of anemia. Sexual hair may decrease in older patients. *The diagnosis is usually made by the physical*

changes and the history, but the metabolism test is valuable as well as the blood cholesterol. If the newer methods of determining thyroid function can be carried out, radioactive iodine uptake is greatly decreased, the level of the serum protein bound iodine is low. These are refinements which, however, are rarely necessary from the practical point of view.

As pointed out in a previous chapter, all patients with spontaneous myxedema should have an x-ray of the skull because in 2 or 3 per cent of patients with chromophobe pituitary tumor, the clinical picture of myxedema may predominate. A long-standing myxedema may adversely affect the hypophysis and in the author's opinion cause a secondary pituitary insufficiency.

THE HEART IN MYXEDEMA

The term myxedema heart has been applied to the dilatation of the heart in myxedema In a majority of cases of myxedema, x-rays of the heart taken before and after treatment show a decrease in size of the heart shadow. In true myxedema, too, there is usually an abnormality in the electrocardiogram, particularly a depression of the T-waves and a slower heart-rate

In severe cases there may be pericardial effusion, in addition to the dilatation of the heart. This has been repeatedly shown by tapping the pericardium and injecting air, showing that the great size of the heart in some cases is not entirely due to dilatation, but to fluid.

Fluid may be found occasionally in the pleural and abdominal cavities and is not necessarily due to congestive heart failure.

Atherosclerosis is probably more common in longstanding myxedema than in the normal population. Calcification of the vessels and peripheral arteries can be noted. This includes atherosclerosis of the coronary arteries.

In older myxedematous patients, but occasionally in those of middle age, angina pectoris may be present before treatment. The outcome of treatment cannot be predicted so great caution should be taken in administering thyroid to these patients regardless of whether or not they have angina of effort. It is best, therefore, to begin with only one-fourth of a grain of desiccated thyroid daily and if this is tolerated over a period of several weeks the dose may be increased to one-half of a grain and gradually up to a grain or a grain and a half. In a few instances even one-fourth of a grain of thyroid may increase the severity or frequency of angina or, on the other hand, ease of intensity of heart pain. In others angina of effort may be completely relieved upon the administration of thyroid. In some instances angina may appear some time after the patient has been satisfactorily treated with desiccated thyroid and the dose may have to be reduced. In our experience quite a number of patients with myxedema who have been brought up to normal metabolic rate and feeling of well being may succumb to coronary thrombosis at a later date.

In cases of myxedema heart with polyserous effusions there may appear to be an associated congestive failure. Desiccated thyroid usually will correct the situation but in some instances the tolerance for thyroid is very poor.

One of the reasons for discontinuance of total thyroidectomy for relief of angina pectoris in thyroid subjects was that in a certain number of patients there came a time when the symptoms of myxedema could not be controlled because of the aggravation of angina of effort or angina decubitus. This became a difficult problem in therapy. In treatment of angina pectoris with radioactive iodine one should not be surprised if such a distressing condition arises at a later date in a small but uncomfortable percentage of patients.

Myxedema may also be associated with other diseases in rare instances such as diabetes or even pernicious anemia. In general, however, myxedema is one of the most satisfactory diseases to treat in medical practice.

HYPERTHYROIDISM

Excessive thyroid function is associated with three types of thyroid enlargement. The first is that of diffuse hyperplasia or Graves' disease. The second type most frequently seen is hyperthyroidism with multiple nodular goiter. There is a third type due to hyperfunctioning discrete adenoma often termed Plummer's disease Graves' disease may be superimposed on nodular goiter so that occasionally such a person with nodular goiter may show

exophthalmos. The patient with hyperfunctioning adenoma does not develop exophthalmos.

Graves' disease is a disease of early and middle life but may occur even up to the age of 80. Toxic or nodular goiter with hyperthyroidism is uncommon before the age of forty and as a rule occurs in the fifth and sixth decades.

Graves' disease is usually easily recognized because of the associated eye symptoms, whereas toxic nodular goiter may be masked because of the lack of great activation so commonly seen in Graves' disease, especially when the goiter is not easily visible. In diffuse hyperplastic goiter or Graves' disease exophthalmos does not always occur and hence the disease is not recognized.

Graves' disease may have a very sudden onset or may be insidious. Perhaps the most prominent symptoms are palpitation, sweating, and weight loss with an increased appetite and food intake Fine tremor, of course, is practically always present and there are varying degrees of muscular weakness particularly of the quadriceps muscles. There may be some atrophy of the muscles of the hands and/or shoulder girdle suggesting progressive muscular atrophy.

If exophthalmos is not present in Graves' disease there is practically always a stare, infrequent blinking, and lid retraction. Retraction of the eyelids suggests exophthalmos even when there is no measurable exophthalmos present.

The thyroid gland is increased in size, fairly firm and

should be easily palpated. It is well to remember that if the thyroid cannot be felt, and this will be discussed later, and if one is confronted with obvious hyperthyroidism with stare and perhaps slight lid lag one must consider factitious hyperthyroidism.

Hyperthyroidism may become very severe although as time goes on we do not see the severe cases as noted fifteen to twenty years ago. This may be because earlier recognition of the disease is taking place. For over ten years we have not seen a patient admitted to the hospital in a thyroid crisis and, of course, since the use of antithyroid drugs, postoperative thyroid storm or crisis does not occur if the patient has been adequately prepared

In extremely toxic cases there may be vomiting and diarrhea. About 5 per cent of the patients with hyperthyroidism show glycosuria and 2 to 3 per cent have definite diabetes mellitus.

Irregularity of the pulse or auricular fibrillation occurs in 5 to 10 per cent of patients with any type of hyperthyroidism. It is more frequent in the older age groups and may be paroxysmal or permanent. By permanent is meant that it is a continuous irregularity until hyperthyroidism is abated.

The heart in hyperthyroidism is not enlarged unless there is congestive heart failure or associated heart disease. The blood pressure is not elevated by hyperthyroidism although the pulse pressure may be increased, in other words true essential hypertension is not caused by hyperthyroidism. There are of course many cases of

exophthalmos. The patient with hyperfunctioning adenoma does not develop exophthalmos.

Graves' disease is a disease of early and middle life but may occur even up to the age of 80. Toxic or nodular goiter with hyperthyroidism is uncommon before the age of forty and as a rule occurs in the fifth and sixth decades.

Graves' disease is usually easily recognized because of the associated eye symptoms, whereas toxic nodular goiter may be masked because of the lack of great activation so commonly seen in Graves' disease, especially when the goiter is not easily visible. In diffuse hyperplastic goiter or Graves' disease exophthalmos does not always occur and hence the disease is not recognized.

Graves' disease may have a very sudden onset or may be insidious. Perhaps the most prominent symptoms are palpitation, sweating, and weight loss with an increased appetite and food intake. Fine tremor, of course, is practically always present and there are varying degrees of muscular weakness particularly of the quadriceps muscles. There may be some atrophy of the muscles of the hands and/or shoulder girdle suggesting progressive muscular atrophy.

If exophthalmos is not present in Graves' disease there is practically always a stare, infrequent blinking, and lid retraction. Retraction of the eyelids suggests exophthalmos even when there is no measurable exophthalmos present.

The thyroid gland is increased in size, fairly firm and



Fig. 6. Recurrent Graves' disease with good sized hyperplastic remnants and severe exophthalmos, with marked lid retraction and peri-orbital edema. Appearance of patient (right) after orbital decompression and relief of hyperthyroidism

hyperthyroidism with hypertension but relief of hyperthyroidism does not significantly lower the blood pressure and may decrease the systolic and raise the diastolic.

Diagnosis

There is little difficulty in recognizing the average case of hyperthyroidism. The borderline cases are the ones we are concerned with in diagnosis. The basal metabolism test is still a satisfactory method of measuring the body metabolism. However, there are certain drawbacks. First, certain nervous patients cannot adapt themselves to the metabolism tests resulting in an elevated basal metabolic rate. Sometimes on repeated tests over two or three days a normal test may be obtained. If the picture is not clear-cut, the patient may be given a heavy dose of sedative early in the morning in amounts equivalent to 3 grains (rarely more) of barbiturates such as seconal or nembutal and the metabolism test taken when the full effect of the hypnotic has taken place.

There are several other conditions besides hyperthyroidism which will give a high basal metabolic rate. Aortic stenosis is known to do this. Pheochromocytoma, a rare disease, may be associated with a high metabolism even between paroxysms of hypertension. If the tumor secretes norepinephrine only there could be little rise in the basal metabolic rate whereas epinephrine has a greater capacity to increase metabolism. Leukemia may also cause an elevated basal metabolic rate.

In some cases with high metabolic rates where hyper-

thyroidism does not seem clinically definite Bartels has employed intravenous pentothal anesthesia and a metabolism taken by the anesthetists with a closed circuit. The metabolism will remain high in aortic stenosis, pheochromocytoma, leukemia or factitious hyperthyroidism even under sedation, but will be normal if due to emotion.

It seems needless to mention the fact that leaks in the metabolism apparatus will give rise to high metabolic rate and that worn-out soda lime will give low metabolic readings because of the failure of diminution in the volume of gas in the apparatus by replacement of oxygen with carbon dioxide.

Anxiety states occurring in people with nodular or colloid goiters often raise the question of hyperthyroidism. The symptoms should not be confused with true hyperthyroidism, but unfortunately they often are, and enlargements of the thyroid are removed without improvement of the patient who is suffering from purely the anxiety or nervous symptoms.

The use of radioactive techniques in the diagnosis of hyperthyroidism is a refinement but is hardly necessary in 95 per cent of the cases one encounters. In fact it is dangerous to make a diagnosis with the use of radioactive iodine without full consideration of the patient's symptoms, his metabolism and physical findings. There are certain conditions which increase the avidity of the thyroid for iodine or decrease it. Previous use of iodine, antithyroid drugs or cholecystograms, urograms or other

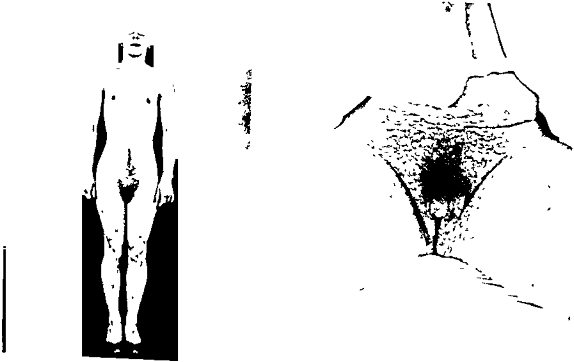


Fig 7 Acquired adrenogenital syndrome due to hyperfunctioning adrenal cortices. Female, age 24. Never menstruated Enlarged clitoris. Urinary 17-ketosteroids 58 and 60 mg. per twenty-four hours Height 62¾ inches. Epiphyses closed (See Figures 8 and 9)

severe forms of hyperthyroidism, however, there is usually a rebound shortly after antithyroid drugs are administered.

If surgery is to be performed, antithyroid drugs should be given until the metabolism is normal. The general consensus now seems to be that antithyroid therapy followed by subtotal thyroidectomy is indicated in patients before the age of 45 to 50 and in all cases of nodular goiter with hyperthyroidism.

There is still some fear of late malignancy in patients with Graves' disease treated with radioactive iodine. How real this threat is still undetermined. Radioactive iodine is being used by some in the younger age group where the danger has been considered the greatest. Radioactive iodine is not indicated in nodular goiter with hyperthyroidism or in the hyperfunctioning adenoma.

Radioactive iodine therapy is quick, easily administered, and results are generally good. The incidence of myxedema, however, will probably turn out to be about the same or greater than following subtotal thyroidectomy. There is one advantage in radioactive iodine therapy; namely, that postoperative tetany or paralysis of vocal cords does not occur.

Postoperative tetany or vocal cord paralysis occurs most frequently in reoperated cases and radioactive iodine, therefore, can be used in recurrent cases if the condition is severe enough to warrant it. In milder recurrences administration of iodine alone is often sufficient. It should not be forgotten that with higher voltage

procedures in which iodine compounds are used will cut down on the radioactive iodine uptake and such tests should be postponed for 6 to 8 weeks. And, of course, there is a variation in normals. Above average radioactive iodine uptake in a borderline case may also lead to the wrong diagnosis.

The hyperfunctioning gland of Graves' disease will take up more radioactive iodine than the normal gland. The nodular goiter with hyperthyroidism will also show in some cases only a slight increased uptake so that it is not as satisfactory a method for diagnosis in this type of goiter.

Treatment

The treatment of hyperthyroidism is gradually changing. There are numerous antithyroid drugs available, none without a small incidence of toxic symptoms, particularly depression of the white count and agranulocytosis. The decision as to what type of treatment should be given depends on many circumstances. Lugol's solution is still a good form of therapy in mild hyperthyroidism; it is without danger and should not be completely discarded. It may be valuable as a therapeutic test, too, in Graves' disease it should return the metabolism to normal in cases in which the latter is not over plus 30 per cent.

The use of antithyroid drugs can be tried and in Graves' disease with glands estimated to be only slightly enlarged it may cause a permanent remission if given over a period of six months to a year. In moderate or

severe forms of hyperthyroidism, however, there is usually a rebound shortly after antithyroid drugs are administered.

If surgery is to be performed, antithyroid drugs should be given until the metabolism is normal. The general consensus now seems to be that antithyroid therapy followed by subtotal thyroidectomy is indicated in patients before the age of 45 to 50 and in all cases of nodular goiter with hyperthyroidism.

There is still some fear of late malignancy in patients with Graves' disease treated with radioactive iodine How real this threat is still undetermined. Radioactive iodine is being used by some in the younger age group where the danger has been considered the greatest. Radioactive iodine is not indicated in nodular goiter with hyperthyroidism or in the hyperfunctioning adenoma.

Radioactive iodine therapy is quick, easily administered, and results are generally good. The incidence of myxedema, however, will probably turn out to be about the same or greater than following subtotal thyroidectomy. There is one advantage in radioactive iodine therapy, namely, that postoperative tetany or paralysis of vocal cords does not occur.

Postoperative tetany or vocal cord paralysis occurs most frequently in reoperated cases and radioactive iodine, therefore, can be used in recurrent cases if the condition is severe enough to warrant it. In milder recurrences administration of iodine alone is often sufficient. It should not be forgotten that with higher voltage

x-ray therapy some cases of Graves' disease could be adequately taken care of.

In preparation of patients for subtotal thyroidectomy, propylthiouracil in 200 to 300 mg. doses is administered until the basal metabolic rate is normal. A rule of thumb is that it should take as many days as the per cent elevation of the metabolism to bring the latter down to normal. In hyperthyroidism due to nodular goiter, the rate of decreasing the basal metabolic rate may be much longer.

If no progress is made in a month on administering antithyroid drugs the dose may be increased. In fact, recently, doses of 1 gm. a day have been administered with faster lowering of the basal metabolic rate.

The patient should be advised regarding the toxic symptoms of antithyroid drugs. These consist principally of fever, sore throat, skin rash, aches and pains, enlargement of lymph nodes, and agranulocytosis. In many instances, routine white counts taken during administration of antithyroid drugs may decrease down to 4,000 per cubic millimeter but if the differential count shows a normal number of polymorphonuclear leukocytes, the medication can be continued.

If propylthiouracil causes toxic symptoms, which it may do in 1 to 2 per cent, another antithyroid drug can be tried, which may not be toxic. This is frequently the case and in some instances, a third antithyroid drug will successfully reduce metabolism without toxic symptoms. There are several widely used antithyroid drugs now, among which are the following: tapazole, neomercazole and itrumil. Treatment of toxic symptoms of antithy-

roid drugs with agranulocytosis is prompt use of penicillin, and possibly streptomycin.

When the metabolism is reduced to normal in hyperthyroidism with antithyroid drugs in a case of a patient with nodular goiter in hyperthyroidism, iodine need not be given but it is probably desirable to stop the antithyroid drug and continue iodine for one week. It is definitely indicated in Graves' disease for the reason that the gland involutes under iodine and is more readily handled by the surgeon, not being so friable or hemorrhagic.

If the hyperthyroid patient has evidence of heart failure or auricular fibrillation, it may be treated as ordinary heart failure if the situation is serious enough to warrant it. However, as soon as the effect of antithyroid drugs comes about, say in ten days to two weeks, there is a definite improvement of congestive failure when present. If the patient cannot be under observation, digitalis can be prescribed in the usual digitalizing doses and the low sodium intake with or without diuretics may be used if the situation is urgent or might become worse at home. In severely toxic patients with Graves' disease who cannot be hospitalized, iodine and antithyroid drugs should be given simultaneously from the very beginning. The administration of iodine will have an immediate effect before the antithyroid drugs can effectively decrease thyroid hormone output. When iodine and antithyroid drugs are given together it will take considerably longer to reduce the metabolism to normal.

Patients with Graves' disease who receive radioactive

iodine should be observed and not too large doses given because of a possible increase in the release of thyroid hormone and a severe thyroid storm follow. This can easily be obviated by continuing iodine and the full dose of antithyroid drug for several weeks.

The practicing physician may have the responsibility of following up patients after a subtotal thyroidectomy or the use of radioactive iodine. Metabolism tests every three months for the first year are probably desirable not only for the worth of the metabolism itself but for the purpose of seeing the patient and determining his condition. Desiccated thyroid can then be administered if necessary, or symptoms of tetany controlled if present.

TREATMENT OF EXOPHTHALMOS

Exophthalmos may improve after successful treatment of hyperthyroidism but the improvement is frequently due to loss of lid retraction because in measuring the protrusion of the eyeball with the exophthalometer there may be little or no change.

The exophthalmic syndrome may occur without hyperthyroidism, or when slight hyperthyroidism exists the exophthalmos may be all out of proportion to it. Exophthalmos may be unilateral only.

Exophthalmos may progress slowly or fairly rapidly, *in fact in some instances it is referred to as malignant.* Treatment, therefore, is desirable if not imperative in some cases. Bilateral orbital decompression may be car-

ried out by a neurosurgeon and an excellent result can be anticipated in over 50 per cent, while satisfactory improvement is the rule.

More recently, roentgen therapy to the pituitary area has been reported as being successful from several centers. Even the retro-orbital space has been irradiated. Apparently the best results are in those cases which have existed a year or less. Adequate dosage is required; we are currently using 4,000 tumor dose roentgen units by the rotational method.

Desiccated thyroid may be given up to 6 grains a day with some improvement in a few cases, but in general the results are disappointing.

FACTITIOUS HYPERTHYROIDISM

While this condition is comparatively rare, yet it occurs frequently enough to be on the alert for its possibility. The clue to the situation is usually found in the fact that the patient may have a very marked hyperthyroidism with all the classical features except exophthalmos and enlargement of the thyroid gland Lid retraction may be present and suggest exophthalmos. Patients who take desiccated thyroid without telling the physician may use various tricks in obtaining it, even when admitted to the hospital. Careful observation for this possibility should be undertaken. If desiccated thyroid is stopped, the metabolism will drop from high values down to normal within a period of a week. One of the definite

values of radioactive iodine uptake is in the detection of *factitious* hyperthyroidism, for the uptake of iodine in the thyroid gland of a patient taking large doses of desiccated thyroid will be very low and in a myxedematous range.

The reasons given by patients who surreptitiously take thyroid are very vague as a rule and little can be ascertained in regard to the psychological reason behind it. Often it is done to feign illness, other times it is taken for the pep which it may give them, or to avoid obesity. Doses of 10 to 20 grains a day are not uncommon.

PREGNANCY

Pregnant women who have Graves' disease can be given antithyroid drugs and successfully operated on. The salvage of live babies is greater when thus treated than without treatment. There is little danger to the fetus from the administration of antithyroid drugs. Whatever danger exists is less than having the mother go through the delivery with possible loss of the child.

CHAPTER IV

PARATHYROID GLANDS

The purpose of the parathyroid glands is to secrete parathyroid hormone which maintains the proper calcium-phosphorus ratio in the blood and tissues with which the skeleton can adapt its architecture in varying conditions. No definite interrelationship has been demonstrated between the pituitary gland and the parathyroid gland. The parathyroid hormone, or parathormone is not necessary for life.

The action of the parathyroid hormone is considered to be on two sites. The first is the kidneys where it enhances the excretion of phosphate by decreased tubular resorption of phosphorus after the filtrate has passed the glomerulus. When the excretion of phosphorus is increased, the serum phosphorus of the blood is lowered. By some unknown mechanism, unless it be from the second action (below), this fall in phosphorus causes the serum calcium to rise in response.

With the increase in serum calcium there is an increased renal excretion of calcium. An important phenomenon to remember, however, is that before there is

an elevation of serum calcium above normal there has already occurred an increased calcium excretion in the urine. In order to supply calcium for the increased excretion, the bones may be drawn upon for calcium if the daily intake is not sufficient to balance the loss.

The second site of action is probably directly upon the bones themselves by liberating the calcium through increased osteoclastic activity. The entire mechanism, however, is still to be completely understood.

HYPERPARATHYROIDISM

An increase in the excretion of parathyroid hormone occurs in either hypertrophy and hyperplasia of all parathyroid glands or in a hyperfunctioning adenoma of one parathyroid gland.

As a result of an excessive secretion of calcium, kidney stones may form or there may be a thinning of the bones. Occasionally the increased excretion of calcium is accompanied by polyuria such as occurs with an increased excretion of glucose. Polyuria, therefore, may be the first and sometimes the only symptom of hyperparathyroidism. In cases showing considerable calcium excretion the urine may actually be milky from the high concentration of calcium in it.

Kidney Stones

Renal colic due to kidney stones may thus be the first symptom of hyperparathyroidism. The number of pa-

tients with kidney stones who have hyperparathyroidism is estimated to be around 3 to 5 per cent. Thus the routine estimation of blood calcium and phosphorus in patients with kidney stones or a history of renal colic is advisable, for otherwise a good many cases of hyperparathyroidism may be overlooked.

Bone Disease

Loss of calcium from the bone leads to considerable rarefaction of the bones and in some cases bone cysts. The latter may occur in the jaw bone. These are giant cell types of tumor and may occur without skeletal involvement. The cysts occurring about the teeth known as epulis should always raise the question of hyperparathyroidism. The whole cranial vault may show thinning of bone and there may be loss of lamina dura about the teeth.

In addition to the diffuse decalcification of the skeleton there may be softening and bending of the long bones or ribs. The cortices are usually somewhat thin. There may be pseudofractures which are characterized by lines of increased density radiating from the cortex representing the junctions of the edges of the pseudofractures. The vertebrae, too, may show thinning, mottling and often compression with wedge-shaped or codfish type of vertebra due to herniation of the nucleus pulposus.

A condition known as osteitis fibrosa generalisata or cystica due to multiple fibrosed and cystlike areas in the bone may occur in hyperparathyroidism. These are

particularly prone to occur in the region of the pelvis.

Even without fractures or collapse of vertebrae there may be bone pain which is rather indefinite. Thus indefinite bone pain or the other symptoms related to the abnormal skeleton may be sufficient reason for investigating the possibility of hyperparathyroidism.

Eye Changes

The eyes as a rule show little on clinical examination but slit lamp investigation may reveal that the conjunctiva at the region of the palpebral fissure may contain small glass-like particles. Occasionally the cornea shows changes of gray granular epithelium and subepithelial deposits running consecutively. This finding is not pathognomonic as it may be found in other conditions with hypercalcemia.

Myotonia

Occasionally on clinical examination there may be considerable hypotonia of the muscles with decreased response to galvanic stimulation.

Acute Hyperparathyroidism

The above are often the findings in chronic hyperparathyrodism but there is an acute or severe type which has often been called "hyper-hyperparathyroidism" or parathyroid poisoning.

In this severe type of hyperparathyroidism the patient may not be seen until in a very critical condition. The serum calcium is exceedingly high, there may be con-

siderable dehydration, oliguria, anuria, followed by renal failure, uremia, and eventually death. It is doubtful whether many of these cases are diagnosed unless there has been a previous history obtainable or if by chance a blood calcium is taken.

Blood Calcium and Phosphorus

The normal serum calcium in most laboratories varies between 9.5 mg. per 100 cc. and 10 5 mg. per 100 cc. The inorganic phosphorus should always be taken fasting since food ingestion will decrease its value, whereas the serum calcium is not so affected.

Verified cases of hyperparathyroidism have been reported in which the serum calcium has been as low as 10.5 mg. per 100 cc. In hyperparathyroidism there is not only an elevation of the serum calcium but a decrease or depression of inorganic serum phosphorus.

Diagnosis

Thus with fairly suggestive x-ray findings or in cases of kidney stones known to be composed of calcium, serious attention should be paid to these borderline values, that is, values between 10 5 and 11 mg., and inorganic fasting serum phosphorus values of 3 mg. or lower. In such cases the Sulkowitch test should be done after placing the patient on a low calcium diet for three days. If the Sulkowitch test shows an excessive excretion of calcium in the urine it affords additional evidence for hyperparathyroidism.

particularly prone to occur in the region of the pelvis.

Even without fractures or collapse of vertebrae there may be bone pain which is rather indefinite. Thus indefinite bone pain or the other symptoms related to the abnormal skeleton may be sufficient reason for investigating the possibility of hyperparathyroidism.

Eye Changes

The eyes as a rule show little on clinical examination but slit lamp investigation may reveal that the conjunctiva at the region of the palpebral fissure may contain small glass-like particles. Occasionally the cornea shows changes of gray granular epithelium and subepithelial deposits running consecutively. This finding is not pathognomonic as it may be found in other conditions with hypercalcemia.

Myotonia

Occasionally on clinical examination there may be considerable hypotonia of the muscles with decreased response to galvanic stimulation.

Acute Hyperparathyroidism

The above are often the findings in chronic hyperparathyrodism but there is an acute or severe type which has often been called "hyper-hyperparathyroidism" or parathyroid poisoning.

In this severe type of hyperparathyroidism the patient may not be seen until in a very critical condition. The serum calcium is exceedingly high, there may be con-

Occasionally calcification of other tissues may take place in hyperparathyroidism and be visible by x-ray.

Differential Diagnosis—Osteoporosis

The differential diagnosis of hyperparathyroidism includes osteoporosis, a common condition. Routine determinations of calcium and phosphorus and alkaline phosphatase in the blood are important in osteoporosis because in some instances the bone changes in hyperparathyroidism are indistinguishable from other causes of osteoporosis. There are many cases of osteoporosis, the cause of which is obscure, some are thought attributable to the menopause or ovarian insufficiency such as seen in ovarian agenesis or in female eunuchoidism. Osteoporosis is fundamentally a failure to lay down matrix, in other words a decrease in osteoblastic activity as compared to osteomalacia in which there are plenty of osteoblasts but failure of calcification.

Among the diseases in which osteoporosis occurs are Cushing's disease, acromegaly, hyperthyroidism, old age, malnutrition, vitamin C deficiency, and disuse. In an occasional male or sometimes a female without any of these disorders, osteoporosis may occur and is, naturally, termed idiopathic.

Osteomalacia

Osteomalacia of adults, sometimes referred to as secondary hyperparathyroidism, is a comparatively rare condi-

It was stated previously that before the serum calcium is elevated in the blood as a result of increased parathyroid secretion, as shown by experimental injection of the parathyroid extract, there is increased excretion of calcium. Thus it can be seen that a patient may well have hyperparathyroidism of mild degree without significant elevation of the serum calcium but in these cases there should be a lowered inorganic phosphorus. Hence, several observations should be made over a period of a few months because by so doing, a higher serum calcium may be obtained at one time or another, sufficient to warrant a diagnosis.

Surgical removal of a parathyroid adenoma should be carried out promptly because the continued excretion of excess calcium through the urine may cause renal insufficiency which may be irreversible.

Renal Insufficiency

When renal insufficiency occurs in this disease, the usual depression of the serum inorganic phophorus may not occur, thus making it more difficult to make a definite diagnosis. In such cases a decision will have to be made on relatively higher serum calcium and on other clinical or x-ray findings.

Calcinosis

Calcium when excreted in excess in the kidney may be deposited within the tubules and cause nephrocalcinosis.

bowel, the serum calcium will eventually fall again in spite of the intense activity of the parathyroid glands.

Four Types of Blood Changes in Osteomalacia. There are four types of chemical change in the blood in osteomalacia which can be accounted for and these will be enumerated here. First, with a normal parathyroid response to calcium deficiency the blood calcium is immediately maintained at a normal level while the inorganic phosphorus is decreased. Second, if, however, the normal parathyroid response exists but is ineffective because of a paucity of available calcium, then the calcium and phosphorus will both be low. Third, if there is an inadequate or absent parathyroid response, the calcium will remain low and the phosphorus may be normal or may later become decreased if there is a paucity of available calcium phosphate. Fourth, when renal failure occurs, the phosphorus may be increased and the calcium may be normal or decreased, but this is not to be particularly expected in osteomalacia unless the condition is due primarily to renal disease.

The alkaline phosphatase is likely to remain normal in the first instance, increased in the second, and increased in the third and fourth situations.

Chemical osteomalacia, that is, blood changes not necessarily accompanied by detectable bone change but often with clinical tetany, is seen particularly in hospital practice in patients who have sprue or in cases in which a considerable amount of the small intestine has been removed for ileitis. It may be a most difficult situation to control.

tion in this country but rickets in childhood is essentially osteomalacia. It may occasionally occur as a result of sprue, chronic pancreatitis or idiopathic steatorrhea in children or adults. Some cases are caused by renal disease either from glomerular damage, which often gives rise to renal rickets, or from tubular disease, a special form of kidney disease in which there is withdrawal of calcium from bones to act as a base because of the failure of the kidney to form ammonia for this purpose.

Osteomalacia then may result either from malabsorption of calcium or loss of calcium. This stimulates increased osteoblastic activity. The stimulus to osteoblastic activity is a low serum calcium. The low serum calcium also is a stimulus to parathyroid gland activity and in cases of osteomalacia there may be fairly large parathyroid glands which in turn because of increased secretion of hormone may bring the serum calcium to normal and cause a higher excretion of phosphorus in the urine. Thus the finding in the blood of a normal serum calcium and a low serum phosphorus is indicative of osteomalacia. There is an increase in osteoblastic activity, because the blood alkaline phosphatase is increased.

In some cases of excessive urinary calcium loss or intestinal malabsorption the parathyroids do not or cannot for one reason or another respond to the decreased serum calcium. If the parathyroids can respond they will cause a return of the serum calcium to normal but the inorganic phosphorus in the serum will be low, as stated above. This can continue only until the calcium reserve is very low and if calcium is not absorbed by the

failure. A high fluid intake including intravenous saline solution is required. The diet should be low in calcium, not more than 250 mg. a day. This type of treatment should be carried out a few days, at least, before parathyroid surgery is contemplated. The level of the alkaline phosphatase in the blood is often an index of the amount of bone involvement in hyperparathyroidism. Patients with kidney stones and no other manifestation of hyperparathyroidism may not have an increase in the alkaline phosphatase. The level of the alkaline phosphatase is an index of osteoblastic activity of the bone. This results from an attempt to replace bone that has been decalcified and destroyed by osteoclasts. If the patient has an extremely high alkaline phosphatase, around 40 or 50 Bodansky units per 100 cc., and if there is evidence of considerable decalcification of bone, one may expect, following removal of parathyroid adenoma, an acute hypocalcemia and tetany which can only be controlled by intravenous infusion of calcium. What probably happens under these circumstances is that bones being avid for calcium, there is a rush of calcium from the serum to the bones, instead of excretion of calcium in the urine. Shortly after removal of the parathyroid adenoma, excess calcium in the urine rapidly decreases or is absent.

The surgical treatment of the parathyroid adenoma should be carried out by a surgeon especially skilled in handling these cases. This is advisable because about 10 per cent of parathyroid adenomas may be located in an aberrant position or actually inside the chest. Some

Vitamin D in large doses, up to 400,000 units a day, with as much calcium orally as the patient can tolerate may increase the absorption rate of calcium and control the symptoms of tetany.

Further, in the differential diagnosis of hyperparathyroidism, one must always consider vitamin D poisoning. In view of the practice of giving large doses of vitamin D for arthritis, a custom which is decreasing but still going on, the serum calcium may be elevated to considerable height and if kidney function is below standard there may be areas of calcification throughout the body as well as the kidneys. The history is usually obtainable in these cases so that the diagnosis may be not too difficult, but in some cases in which the patient is in the semicomatose condition from hypercalcemia, the history may not be elicited and one might well suspect hyperparathyroidism because of the high serum calcium. In these cases the inorganic phosphorus of the serum should be somewhat elevated in view of the increased absorption of calcium and phosphorus but if the condition has been long-standing there may be renal failure and very high inorganic phosphorus determination. Thus it can be seen that the diagnosis may easily be confused with that of hyperparathyroidism.

Treatment

When parathyroid poisoning is present which is manifested by a high serum calcium level of 17 mg. per 100 cc. or over, there is always danger of impending renal

high serum alkaline phosphatase preoperatively, intravenous calcium may have to be given continuously until there is sufficient absorption of calcium by the bones to allow the serum calcium to be maintained above the level which produces tetany.

In summary, hyperparathyroidism should be suspected in any patient with unexplained polyuria, and a history or demonstration of kidney stones (calcium). Bone disease such as absent lamina dura, osteoporosis, bone cysts or epulis and giant cell tumor, should be investigated to rule out hyperparathyroidism. Obscure bone pain and spontaneous fractures also may be due to this disorder. Marked muscular hypotonia is occasionally a sign of hyperparathyroidism.

PRIMARY HYPOPARATHYROIDISM

Hypoparathyroidism is observed more frequently following surgery on the thyroid gland, but it may occur idiopathically although this is extemely rare. Idiopathic hypoparathyroidism may or may not be associated with manifest tetany. Tetany not only is due to hypoparathyroidism but may be caused by other hypocalcemic conditions. Tetany may also be caused by alkalosis, from hyperventilation, and vomiting as a result of pyloric obstruction or from excessive sodium bicarbonate intake. It may also be associated with renal abnormalities especially of the congenital, obstructive types, and polycystic kidneys.

have been located as far down as the heart. A few of these tumors may be present in the thyroid gland itself and the thyroid might have to be sectioned to locate a parathyroid adenoma if it is not found in its usual location. Parathyroid tumors average about 7 gm. in weight but have been reported as large as 120 gm.

In rare instances parathyroid adenoma might be identified by x-ray or, occurring near the esophagus, by indentation of the esophagus following barium.

Another reason for special competence in operating upon patients with hyperparathyroidism is the recognition of enlargement of all parathyroid glands in which partial resection of all glands is necessary. Removal of one gland is of no benefit, and considerable experience is necessary to judge the amount of tissue to remove from these hypertrophic glands. When a parathyroid tumor is present, the other glands may look normal or atrophic. The approach to the parathyroid tumor can often be suspected by the evidence of increased blood supply to the region where the parathyroid adenoma exists.

Postoperative care is important. A good many of these patients will have temporary parathyroid deficiency and will require calcium and vitamin D or dihydrotachysterol. It is advisable, however, to withhold these medications if tetany is not too severe because the underactive hypoplastic parathyroids remaining should be stimulated to produce hormone but will be retarded from so doing if vitamin D and calcium are supplied. It has already been stated that in rare instances, when there has been a very

calcium deficiency. The presence of a thyroid scar should always make one suspicious of parathyroid tetany. In the postoperative thyroid cases the only symptoms may be a tingling of the face and some tightness or spasm of the hands or feet because of a relatively mild degree of hypocalcemia.

A positive Chvostek is indicative of tetany but is not pathognomonic. It may occur in tetany without other manifestations. When present with Trousseau's sign, tetany is likely. In 25 of 500 medical cases Chvostek's sign was found to be present without hypocalcemia or tetany.

Cataracts

Untreated, hypoparathyroidism leads eventually to cataract formation. We have seen 2 patients in whom cataracts were the first clinical evidence of hypoparathyroidism, although in one case not even a positive Chvostek or Trousseau's sign could be elicited. In both cases there was a low serum calcium and elevated serum phosphorus. Thus the presence of cataracts should make one consider hypoparathyroidism as the cause and necessitate a blood calcium determination.

Intracranial Pressure and Calcification

Long-standing hypoparathyroidism may also lead to increased intracranial pressure with choked disks and headache, with or without epileptiform attacks. Thus it

Manifestations of Tetany

The symptoms of acute tetany, whether the latter be due to parathyroid deficiency or other causes, are manifested by numbness or tingling of the upper lip, side of the face, or extremities, sometimes contractions of eyelids and facial muscles in which the corners of the mouth may be drawn upward. Carpopedal spasm may occur and be unilateral or bilateral. Adductor muscles of the thighs may be paroxysmally spastic. Laryngeal spasm may occur with a loud inspiratory crow, lasting minutes to hours. When tetany is severe, epileptiform seizures indistinguishable from epilepsy may occur, lasting for a few seconds or periodically for hours. Attacks may start in the hands, and spread all over the body. There are other signs of severe acute tetany such as strabismus, inequality of pupils, difficulty in swallowing, and cramplike pain in any or all muscles which may be associated with tonic or clonic contractions, either unilateral or bilateral. Opisthotonos may occur in children

In chronic hypoparathyroid tetany the manifestations may occur only with effort or sudden change of position, such as getting out of a chair and standing up. For some reason or other, tetanic spells may come on without reason, the patient being free of attacks at other times.

Diagnosis of hypoparathyroidism may be difficult at the time of seizures but later, the past history should be revealing. There is no harm in giving intravenous calcium even when the condition is found later not to be due to

reduced. Milk itself supplies about 1.5 gm. of calcium lactate in one quart.

In addition, either dihydrotachysterol (AT-10) or vitamin D can be administered. The treatment consists of giving dihydrotachysterol, 1 to 3 cc. a day, until the serum calcium becomes normal. If serum calcium determinations are not available, the Sulkowitch test can be used (see Laboratory Procedures). When calcium appears in the urine it is likely that the serum calcium will be at a fairly normal level unless in rare instances there may be an unusually low threshold of the kidney for calcium.

Vitamin D in capsules containing 50,000 units may also be given for the control of chronic hypoparathyroid tetany in doses of 150,000 units a day until the calcium is normal, which will usually occur within a week, when it can be reduced to 100,000 or 50,000 units a day as is necessary. Vitamin D is less expensive than dihydrotachysterol and equally effective. Since both of these preparations facilitate the absorption of calcium from the gut, an added amount of calcium should be given as described above. Otherwise calcium may be withdrawn from the bones.

If hypoparathyroidism is adequately treated, cataracts will not develop and the patient may lead a very normal life without further complications. Calcification of the brain has not been observed in patients who have been adequately treated for many years. Convulsive seizures will cease unless there is also associated true epilepsy.

is desirable to determine the serum calcium on patients with epilepsy, particularly in children and especially those who have a positive Chvostek's sign. Another feature of chronic hypoparathyroidism is calcification at the base of the brain. A fairly characteristic rounded shadow occurs above and somewhat behind the sella turcica and is almost pathognomonic of hypoparathyroidism. It is occasionally mistaken for a calcified tumor on x-ray examination.

The blood findings in hypoparathyroidism are lowering of the serum calcium often to values of 6 mg. per 100 cc. and a corresponding increase in serum phosphorus, reaching 6, 7 or 8 mg. per 100 cc. The alkaline phosphatase is normal or below normal. In some instances there may be only 1 or 2 mg. decrease in serum calcium. In these cases the serum phosphorus may be much higher. It is really the calcium phosphorus ratio that is important. Serum phosphorus should be done on patients who are fasting. (See Laboratory Procedures.) The Sulkowitch test is negative in this disease when it is untreated.

Treatment

The treatment of hypoparathyroidism is the administration of calcium. Calcium lactate is the most easily tolerated of all calcum preparations. Doses of 1 to 2 heaping teaspoonfuls of calcium lactate three times a day dissolved in any warm or hot solution is palatable. Occasionally this quantity of calcium may cause some looseness of bowels, in which case the dose may have to be

clinical syndromes may be attributed to disorders of the adrenal glands.

The adrenal glands consist of the cortex and the medulla, which are embryologically of different origin, the cortex arising from splanchnic mesoderm and the medulla from the ectoderm. The adrenal cortex elaborates a variety of hormones, whereas the medulla secretes only two recognized hormones, namely, epinephrine and norepinephrine. So far as is known, there has been no proven interrelationship between the cortex and the medulla, although they are anatomically a unit.

There are several zones in the adrenal cortex, three recognized and a fourth is questionable Since there are numerous hormones elaborated in the adrenal cortex, attempts to locate the origin of the various hormones are still not well defined but there is hope that such will be accomplished.

SEVERAL TYPES OF ADRENAL CORTICAL HORMONES

The adrenal cortex secretes hormones of different end organ reactions, such as (1) those similar to cortisone or hydrocortisone, and these are often called sugar hormones. These hormones have an anti-inflammatory, carbohydrate metabolism inhibiting, and lympholytic action These sugar hormones antagonize growth hormone and insulin and also in all probability other metabolic processes; (2) testosterone-like or anabolic hormones (an-

CHAPTER V

DISEASES OF THE ADRENAL GLANDS

Addison's disease is the best known of adrenal disorders. Long before Addison first described this condition it had been recognized that certain sexual abnormalities might occur with tumor or hypertrophy of the adrenal glands. These abnormalities can be classified under the general term of the adrenogenital syndrome. Bittorf preceding this described feminization of males associated with adrenal neoplasm. Cushing described a situation which he believed was of pituitary origin but which was also recognized to arise from tumors of the adrenal cortex and the clinical findings were different from other conditions associated with hyperfunction of the adrenal cortex. Thus quite divergent clinical pictures may arise from diseases affecting the cortex of the adrenal glands. From the medulla still another syndrome was described by Labbé and others in 1922 in which there was hyperfunction of tumors composed of medullary tissue, namely, pheochromocytoma. As will be shown later, still other

THE ADRENOGENITAL SYNDROMES

The adrenogenital syndrome found at birth or occurring within a few years thereafter is the result of hyperplasia or hyperfunction of the adrenal cortex as regards the excess elaboration of an androgenic type of hormone. The physical abnormalities in the adrenogenital syndrome depend on the sex of the individual as well as the time of onset. The signs and symptoms are those of precocious sexual and somatic development in the male fetus or young boy or masculinization and various degrees of increased somatic development in female fetus, young or adult females.

The importance of recognizing the adrenogenital syndrome in infancy lies in the determination of the actual sex of the individual. If excess androgenic function of the adrenal cortex takes place early in fetal life, it influences the development of the female sexual organs. If it occurs early, there is retarded development of the duct system, ovaries are rudimentary and the vagina does not develop. At birth the clitoris is enlarged, there may be hypospadias, a rudimentary prostate, and of course evidence of masculinization, although this may take some time to develop.

Should the overactivity of the adrenal cortex occur late in fetal life of the female, the mullerian duct system is developed, the ovaries may remain rudimentary, but the vagina is visible and may open into a urethral hypospadias. The clitoris also is enlarged and hypospadias

drosterone, androsterone-dehydroandrosterone) which cause nitrogen retention for growth or anabolic purposes and if elaborated in sufficient quantities may masculinize the female or cause precocious development of the male child; (3) salt regulating or mineral hormones whose *function seems to be the conservation of salt;* (4) estrogenic hormones which are of importance from the point of view of causing feminization of the female when elaborated in excess quantities in the absence of any great competitive action of testosterone-like hormone; (5) progesterone (pregnanediol, pregnantriol) may be excreted in cases with adrenal tumor or hyperplasia of the cortex.

Although not conclusively proven, it is probable that hydrocortisone represents the true secretion of the adrenal cortex as regards the sugar type of hormone. The nature of the androgenic hormone is in all probability one of the three mentioned above. A very potent electrolytic or mineral hormone has been isolated only recently by Simpson and others (1952) and has been named aldosterone.

Over thirty compounds have been isolated from the beef adrenal but these compounds are not necessarily the ones elaborated primarily in the adrenal cortex and may represent only metabolic breakdown products. The form of estrogenic hormone is not definitely established but there is little doubt about its estrogenic function.

Let us now consider the disorders of the adrenal gland which are commonly met with at birth or shortly thereafter.

Thus a girl born with the adrenogenital syndrome may show an enlarged clitoris and may be mistaken for a male with undescended testes and thus be raised as a boy. The determination of the sex in such cases is difficult, but the bone age of the individual is usually advanced and, if possible, the urinary 17-ketosteroids are increased far above the usual average for the age of the infant or child. Such would not be present in a cryporchid boy with hypospadias.

Often these conditions are not recognized until childhood or even later in life. Due to the secretion of androgens by the adrenal cortex, there is an increased growth rate and a tendency to put on weight, some of the individuals being quite obese. There is usually increased hair growth.

In the young male with adrenogenital syndrome there is precocious development of the penis and pubic hair, along with advanced bone age and early and increased growth rate. The testes, however, in the adrenogenital syndrome are not proportionately enlarged as compared to the size of the penis.

Feminization of the female or male in childhood may occur from malignant disease of the adrenal cortex due to excess elaboration of estrogenic hormones, but as a rule this syndrome is a disease of adults.

A curious situation may occur in children with the adrenogenital syndrome which points to the probability that different hormones may come from different zones in the adrenal cortex. It is well recognized that infants

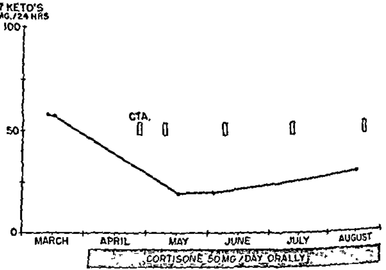


Fig. 9. (Chart) 17-Ketosteroid excretion of case shown in Figures 7 and 8. In this patient, oral administration of *cortisone* only was effective in relatively small dosage. Patient now maintained on 25 mg. cortisone daily. Intramuscular cortisone, 100 mg daily for one week, may be necessary in some cases to reduce output of 17-ketosteroids, which may then be maintained at a low or normal level with varying doses of cortisone. Menstrual periods are indicated by oblong blocks.

may be present as in the earlier overactivity of the adrenal cortex. The prostate is not enlarged in these cases.

If the overactivity of the adrenal cortex takes place after birth, the müllerian duct system is well developed, the ovaries may remain rudimentary; however, the vagina is present. The clitoris also remains enlarged but there is no hypospadias. The prostate is absent, although maculinization takes place.

Thus a girl born with the adrenogenital syndrome may show an enlarged clitoris and may be mistaken for a male with undescended testes and thus be raised as a boy. The determination of the sex in such cases is difficult, but the bone age of the individual is usually advanced and, if possible, the urinary 17-ketosteroids are increased far above the usual average for the age of the infant or child. Such would not be present in a cryporchid boy with hypospadias.

Often these conditions are not recognized until childhood or even later in life. Due to the secretion of androgens by the adrenal cortex, there is an increased growth rate and a tendency to put on weight, some of the individuals being quite obese. There is usually increased hair growth.

In the young male with adrenogenital syndrome there is precocious development of the penis and pubic hair, along with advanced bone age and early and increased growth rate. The testes, however, in the adrenogenital syndrome are not proportionately enlarged as compared to the size of the penis.

Feminization of the female or male in childhood may occur from malignant disease of the adrenal cortex due to excess elaboration of estrogenic hormones, but as a rule this syndrome is a disease of adults.

A curious situation may occur in children with the adrenogenital syndrome which points to the probability that different hormones may come from different zones in the adrenal cortex. It is well recognized that infants

with the adrenogenital syndrome show increased masculinization either in male or female, at the same time being deficient in the salt retaining hormones; in other words, presenting a picture of acute adrenal or chronic adrenal insufficiency in spite of the fact that there are excessive androgenic hormones. This condition responds to administration of salt, cortisone and desoxycorticosterone just as in Addison's disease itself, but the serious and weakened condition of these children is dependent largely on the absence of the mineral hormone, presumably electrocortin.

Feminization of the male due to adrenocortical cancer is a fairly rare condition. I have seen such a case from malignancy apparently due to Simm's tumor of the kidney. It was metastatic to the liver. The breasts developed and there was testicular atrophy and loss of libido. Urinary studies made at that time (this was some fifteen or eighteen years ago) showed excess estrogen by bioassay.

There are, of course, other causes of gynecomastia in males and adrenocortical carcinoma should not be thought of in every case that comes along. It is obvious that if it is due to carcinoma there must have been a fairly recent development and if the hormonal excretion is sufficient to cause fairly rapid enlargement of the breast there should then be corresponding atrophy of the testes and loss of sexual power. (See chapter on gynecomastia.)

Differentiation between Tumor and Hyperplasia

In the differential diagnosis of adrenogenital syndrome in young females one has to consider first whether the



Fig 8 Result of cortisone therapy on breast development Patient now maintained on 25 mg cortisone daily Normal and regular menstruation (Same patient as shown in Figure 7)

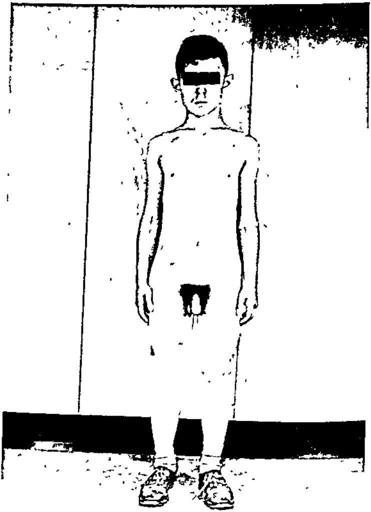


Fig. 10. Congenital adrenogenital syndrome in a boy of 9. Height 59½ inches. Height age 13 years Radial epiphyses closed and no further growth possible Urinary 17-ketosteroids 50 and 57 mg. per twenty-four hours before treatment and 22 mg. per twenty-four hours while on 50 mg cortisone per day. Testes are small compared to size of penis Testes should enlarge and spermatogenesis should take place on cortisone at the usual time of puberty.

condition is due to tumor or adrenocortical hyperplasia. If the child was born with an enlarged clitoris, then one can be almost certain that it is due to congenital adrenal hyperplasia. There are several ways of determining this. First, palpation should be carried out and plain roentgenograms of the adrenal area taken, so that displacement of the kidney or possible calcification in the tumor might be found. Urograms are usually done at the same time that presacral air insufflation is carried out. The latter is an especially excellent method for showing both adrenals. It is not practical to separate or attempt to demonstrate the various steroids which would lead one to suspect a tumor, such as dehydroisoandrosterone. The administration of cortisone will decrease the output of 17-ketosteroids in hyperplasia, but is said not to do so in tumor. Since cortisone given orally is not always effective in reducing the 17-ketosteroid output initially in the adrenocortical syndrome, 100 mg. a day for a period of a week in young adults should bring the excess 17-ketosteroids down to normal, smaller doses of about 50 mg. intramuscularly in children and perhaps 25 mg. in infants.

Treatment

In the treatment of congenital adrenal hyperplasia it is desirable to keep the level of 17-ketosteroids in the normal range and a laboratory for determining the 17-ketosteroids is almost a necessity. If facilities are not available it is then best to treat all cases of adrenogenital syndrome with intramucular cortisone for a week and then administer it orally. Fifty milligrams a day in adults

should keep the 17-ketosteroid excretion down, 25 mg. a day in children and perhaps a lesser amount in infants, but I have had experience with one girl of about fifteen years who required 75 mg. a day orally to suppress the urinary 17-ketosteroids to a normal level.

Improvement with cortisone begins within a few weeks to a few months. Breasts begin to enlarge, menstrual periods may begin, and acne decreases. The theoretical effect of cortisone (or hydrocortisone) is to suppress the output of corticotropins from the anterior pituitary which stimulate the adrenal cortices. This in turn diminishes the excretion of androgenic hormones as well as estrogenic hormones from the cortex which are being excreted in excess but are overshadowed as far as general physical effects are concerned by the androgens. Estrogens, however, being a much more potent inhibitor of the gonadotropic hormones of the pituitary, suppress the latter so that no female characteristics to speak of are present. Once the excessive estrogen is suppressed, the gonadotropic hormones of the pituitary are permitted to function and the peripheral gonads (ovaries) react in the female and thus allow for breast development and normal sexual development in absence of the excess of androgen. The same is true in the male where in all probability estrogens again are secreted which depress the gonadotropic hormones of the pituitary.

It would seem logical, therefore, to try high voltage x-ray over the pituitary in adrenogenital syndrome of this theory is correct. High voltage therapy does work in some cases of Cushing's disease not due to tumor and it would

be, therefore, natural to expect it to be effective in the condition under discussion. On the other hand, we have tried it by using rotational therapy with two million volt x-ray apparatus, giving 4500 roentgen units to the pituitary without significant change in the output of 17-ketosteroids or in the patient's condition.

Treatment of boys with the adrenogenital syndrome is advisable since these boys do not grow to a normal height because of early epiphysial closure. Another reason is probably that fertility may not take place when they become adult, but on this point I do not know whether this is always true. In one case reported by Lisser of an adrenogenital syndrome due to tumor in a young boy, there was spermatogenesis

If normal menstruation occurs after cortisone therapy, the usual dose being 25 to 60 mg a day orally, breast development and feminization should take place, and presumably ovulation. There have not been many reports of long term therapy in females with adrenogenital syndrome; however, one patient became pregnant but miscarried.

It is entirely possible that in the future, bilateral total adrenalectomy may be found desirable in cases of adrenogenital syndrome in order to lessen the intake of cortisone Subtotal resection has been done in the past by the late Dr. Hugh Young of Baltimore. There was a tendency for recurrence of adrenal hyperplasia so that cortisone in all probability would be needed to continue the suppression of the excess 17-ketosteroid secretion if such a procedure were carried out.

Feminization of the male due to adrenocortical carci-

noma should be considered in males who have heretofore been normal but who have lost libido and have had some testicular atrophy and gynecomastia. In such cases there should be little difficulty in suspecting the diagnosis because the secondary evidence of carcinoma may be present, such as loss of appetite, pain and loss of weight. Presacral air injection should demonstrate the enlargement or a tumor due to adrenocortical carcinoma. So far as I know, there has not been reported a case of feminization due to a benign adrenocortical tumor. The adrenogenital syndrome acquired in adult life in the female which is characterized by varying degrees of virilism is usually due to tumor. Differential diagnosis of these cases is discussed under "Hirsutism."

CUSHING'S DISEASE

Cushing's disease is a comparatively rare condition but is of importance in the differential diagnosis of patients with hirsutism and obesity, which are so frequently seen. The manifestations of Cushing's disease are the result of excessive production of adrenal cortical steroids of the cortisone-like types. The disease as first described by Cushing was attributed to a basophilic cell adenoma of the anterior pituitary gland which secreted excessive quantities of corticotropin, thus stimulating the adrenal cortices to produce steroids which are the actual cause of the characteristic syndrome. Later it was shown that tumors of the adrenal cortex which secreted excessive steroids could also produce the condition. Cushing first de-

cribed the disorder as pituitary basophilism but now it s universally called Cushing's syndrome. Some authors)elieve that Cushing's syndrome should be applied to hose cases due to tumors of the adrenal cortex, whereas Cushing's disease should be applied to the cases in which only hyperplasia of the adrenal cortices is present, pre-sumably due to basophilic adenoma.

The basophilic adenomas in the pituitary gland are not uncommon, even in individuals who do not have Cushing's disease. Practically never is the adenoma large enough to cause enlargement of the sella turcica, so that one should not expect any increase in the size of the sella turcica, although in rare instances it has been reported.

Physical Findings

The characteristic roundness of the face in this disease, now so well known to physicians who have administered cortisone in doses sufficient to produce this change, is readily recognized. In addition to the roundness of the face, there is usually an increased growth of hair on the face, which formerly was attributed to androgenic steroids of the adrenal cortex, but now it is well known that not only does cortisone produce roundness of the face but also may stimulate hair growth and cause acne as well. The appearance of the face in Cushing's disease is sometimes described as "pig-eyed" or "moon face." Plethora of the face is usually noticeable and is due to the increase in the hemoglobin and red cells, which may be on the average 10 to 15 per cent above normal.

The fat pad at the nape of the neck in Cushing's disease

is quite prominent and the added obesity of this disorder has a tendency to localize around the shoulders and upper thorax, hence the word "buffalo obesity." A few patients with Cushing's disease may also have considerable abdominal fat.

Striae of the skin, which are characteristically purplish in color, may be present on the arms, the sides of the hips, the legs, or the abdomen, radiating somewhat upward from the pubic area. These vary in intensity and width. They are to be distinguished from the pink striae so commonly seen in young people who have been excessively fat or who have gained weight very rapidly, due undoubtedly to stretching of the skin. The purplish color may persist but tends to decrease if there has been successful treatment. Striae of this type need not be present to establish the diagnosis.

The next obvious physical manifestation frequently seen is ecchymosis of the shins, or, at times, other surfaces of the extremities. In addition to this, the skin is quite thin, often resembling thin cellophane or parchment.

Hypertension is usually present of varying degree. In some instances it may be only around 130/90 or 140/100, while in other cases it may be quite high. Certainly the adrenocortical steroids are probably not the cause of this hypertension but it cannot develop without the presence of these steroids even in normal individuals. As Ingel has pointed out, the adrenocortical steroids are permissive in their action, but not necessarily causative. Considering

the hypertensive familial backgrounds of many patients, it is quite possible that some of the hypertensive states in patients with Cushing's disease may only be aggravated by the development of Cushing's disease. Certainly it is well known that the blood pressure when extremely high does not return to normal even with total adrenalectomy. Changes have been shown to occur in the kidney in Cushing's disease which may account in part at least for the irreversibility.

Symptoms

What kind of a history do patients with Cushing's disease give when seeking examination? After the above description of the physical manifestations of the disease, it is obvious that there may be a variety of complaints. Some complain of obesity, hirsutism, palpitation, shortness of breath and orthopnea if the hypertension is severe; but perhaps the most frequent complaint in woman with Cushing's disease is amenorrhea. Most women who are examined for Cushing's disease have had amenorrhea for some time. However, it is not a necessary accompaniment of Cushing's disease, as fairly well marked cases of Cushing's disease may continue to menstruate, but it is the exception and not the rule.

In men as well as in women, loss of strength and fatigability may be important symptoms. In men there is often a loss of libido with actual testicular atrophy. The nervous or psychiatric disturbances which accompany the administration of cortisone are known to most physi-

cians. These abnormalities are often seen in Cushing's disease, especially mental depression. In our series of cases of Cushing's disease, there have been 6 or 7 markedly depressed patients, 3 of whom have committed suicide, and one who continued to have depression after the successful removal of an adrenocortical tumor.

Laboratory Examinations

There are certain examinations of the blood capable of being carried out in a routine clinical laboratory which are helpful in confirmation of the diagnosis of Cushing's disease. There is usually a slightly elevated leukocyte count, about 9,000 to 12,000. The adrenocortical steroids apparently have a stimulatory effect upon the bone marrow and this has been noted in certain anemias where the administration of adrenocortical steroids increases the red blood cell count and hemoglobin and particularly has it been noted that the blood may improve in Addison's disease or in hypopituitarism upon the administration of cortisone or hydrocortisone, or ACTH, or corticotropins (in hypopituitarism only), which in turn produces cortisone-like substances from the adrenal cortex.

Due to the lympholytic action of adrenal steroids of the cortisone type there is a diminution in the percentage and total number of lymphocytes. The ordinary differential count of blood done in the average laboratory consists of counting 100 cells, but this is not accurate enough if one desires to determine a relative and absolute lymphopenia. At least 500 cells should be counted in different parts of

the slide. A lymphocyte count of 15 per cent or less certainly points to excessive adrenocortical function of the Cushing type. Such is not present in the pure adrenogenital syndrome, but may be in some cases where there is a combined effect on the body from excessive secretion of the androgenic as well as the cortisone-like steroids producing some masculinization as well as cushingoid features. In such cases the lymphocyte count may be down too. The author has noted this in adrenocortical carcinoma causing a mixed syndrome. In active and typical cases of Cushing's disease a lymphocyte count of 8 to 12 per cent is not uncommon.

During a differential count on 500 cells the significance of eosinophilia may be shown in that perhaps one or no eosinophil cells may be noted in counting this number of cells. The total eosinophil count usually reveals 50 or less per cubic millimeter and often there are none to be found whatsoever.

The technique of doing a total eosinophil count requires rigid standards and experience in differentiating an eosinophil from a polymorphonuclear leukocyte which has some eosinophilic granules in it. The true eosinophil will show fairly large granules crowded closely throughout the entire cytoplasm of the leukocyte

Going further into the laboratory diagnosis of Cushing's disease, most patients have glycosuria and/or an elevated blood sugar. In some instances, however, this can be brought to light only by a glucose tolerance test. For routine use the administration of 100 grams of glu-

cose upon a fasting stomach followed by taking blood sugar one and two hours thereafter is of practical importance. Even testing the urine at these intervals may reveal sugar and can be interpreted as evidence of the diabetic tendency. Here again the possibility of the diabetic "anlage" as determined in the history by the presence of diabetes in the family may possibly account for some of the cases of severe diabetes in Cushing's disease.

If one wishes to carry out the study of the carbohydrate mechanism further, insulin may be given at the same time glucose is given. In cases where the disturbance in carbohydrate mechanism is due only to the excess adrenocortical steroid secretion, insulin will not be effective, showing that this diabetic tendency is insulin resistant. Insulin is effective in the clinical diabetes of Cushing's disease and, as stated previously, may be a true diabetes aggravated by excess adrenal steroids.

If laboratory facilities are available for determining 17-ketosteroid excretion, the total 17-ketosteroid excretion will be found elevated in Cushing's disease. The increase in 17-ketosteroids may be derived from an excess secretion of the cortisone-like steroids of the adrenal cortex. In some cases the 17-ketosteroid excretion may be within normal limits. When one recalls that there are many hirsute women without any demonstrable pathology who may have urinary 17-ketosteroids above normal, their value in differential diagnosis of Cushing's disease is limited. There are also methods for estimating the cortisone-like steroids in the urine. These have, in the past, been

rather unsatisfactory due to intricate techniques. However, very low or high values are significant.

X-ray studies are often valuable since considerable osteoporosis of the bone is almost a regular feature in Cushing's disease and has a predilection to attack the lower spine and pelvis, although it may be seen in the skull and other parts of the body. The reason for osteoporosis is somewhat obscure but is considered by some to be due to the anti-anabolic effect of cortisone-like hormones; osteoporosis has also been noted as the result of treatment with cortisone for arthritis or other diseases.

While it is not particularly desirable to administer cortisone and hydrocortisone to patients with Cushing's disease, it may to some extent suppress the output of urinary steroids in the urine if the situation is due to hyperplasia, but will not do so if there is an adrenocortical tumor, either benign or malignant. This is not a practical routine procedure, only of interest from the scientific point of view.

The patient with Cushing's disease may have spontaneous fractures, but in spite of the aforementioned anti-anabolic effect these fractures tend to produce callus and heal The author has seen rib fractures occur spontaneously with abundant callus formation and eventual calcification. This might be explained by the fact that the trauma at the site of the fracture prevents the excessive adrenocortical steroids from acting, and preventing the normal repair mechanism stimulated by the trauma of the fracture.

If Cushing's disease occurs in childhood, it has the opposite effect on growth and bone maturation as compared to the adrenogenital syndrome. There is a retardation of linear growth, the normal value of inorganic serum phosphorus of the child is decreased and the bone age is retarded rather than advanced. Osteoporosis may also be present. In addition, there is retardation of sexual development in both male and female.

Returning to laboratory examinations, there is another abnormality occasionally seen in Cushing's disease, namely, a low serum potassium, a high carbon dioxide combining power and a decreased chloride. This is called hypochloremic alkalosis. Since the advent of cortisone and hydrocortisone, studies on animals and man have shown that there may be an increased loss of potassium, increased loss of chlorides, and the sodium is retained and combined with carbon dioxide. This can be corrected by the administration of chloride and potassium. It is quite unusual for this electrolyte disturbance to produce any serious physical manifestations. Treatment of the disease itself will correct it.

There is little to be learned by other laboratory procedures such as the basal metabolic rate, calcium or phosphorus determinations. Nonprotein nitrogen or urea nitrogen might be investigated in those cases in which there is hypertension or albuminuria.

Tumors, benign or malignant, of the adrenal cortex probably account for about one-fifth to two-fifths of cases of Cushing's disease. Investigation as to the origin of Cushing's disease depends on x-ray studies, especially pre-

sacral air injection if urograms or plain roentgenograms over the adrenal areas do not show a tumor or if it is not palpable. It is to be conceded that in rare instances even presacral air injection may fail to demonstrate a tumor of the adrenal cortex which is no larger than a good sized lime or lemon. Since exploration is being practiced widely in many cases of Cushing's disease, such tumors will be found; if not, removal of the adrenals in part or in whole can be carried out.

Treatment

The author's present procedure is to have presacral air injection carried out and if the adrenals are plainly shown without tumor, then x-ray therapy to the pituitary is recommended providing it is feasible, especially in milder cases. There is little question that the disease can be arrested in some cases with x-ray therapy. Probably one of the reasons it has been given up in some quarters is because inadequate therapy has been applied. At the present time we are using rotational therapy with the two million volt apparatus, directing 4,000 tumor dose units to the pituitary gland. The author is aware that in some centers as much as 6,000 roentgen units (tumor dose) are given in a series of treatments.

In a few instances it has been necessary to forego x-ray therapy because of the inability of the patient to be transported to the two million volt x-ray apparatus, either because of multiple vertebral or other fractures or extreme weakness.

If x-ray therapy is not available, if it has not been suc-

cessful, or if it is impractical to use it, then bilateral adrenalectomy is recommended, total removal of one gland and five-sixths or six-sevenths of the other gland. It is realized that with such a radical procedure as this the adrenal cortical remnant may not function sufficiently. On the other hand, the rationale for total adrenalectomy and maintaining the patient on cortisone is the chance of recurrence if a remnant is left behind. Some believe that 10 to 20 per cent of cases will have a recurrence. This is not surprising in view of the recurrences after partial resection in the adrenogenital syndrome.

Total adrenalectomy has been carried out many times for a variety of conditions since it has been shown that the patients may be maintained adequately on relatively small doses of cortisone, not over 50 mg. a day, and in many instances without the added use of desoxycorticosterone acetate pellets.

In preparation for total adrenalectomy or even a bilateral subtotal adrenalectomy as outlined above, the patient should receive for two or three days before operation 100 to 200 mg. of cortisone acetate or its equivalent in hydrocortisone. This may be given orally or intramuscularly. This should be continued through the operation and gradually cut down after the operation to about 50 mg. per day. Before surgery it is wise to have available hydrocortisone for intravenous use to be given at the rate of 10 mg. per hour for four to five hours, during the operation and shortly thereafter if there is a falling blood pressure to levels below 90 to 100 mm. For alarming and

rapid fall in blood pressure, norepinephrine can be given intravenously in 500 cc. of saline or glucose at the rate of 0.2 micrograms per kilogram of body weight per minute (solution of 1 mg. per liter of saline).

If the operation is done in two stages, for example, one adrenal removed at the first operation, there is little need for preoperative cortisone if it has been well established that a tumor does not exist, and in case both adrenals are shown by presacral air injections. Should exploration prove otherwise, intravenous hydrocortisone can be started at once during the operation, and if possible before the removal of the tumor.

If a total adrenalectomy is carried out, 5 mg. of desoxycorticosterone may be given daily for two days prior to operation and for a few days after operation. There is no doubt that the conservative procedure is a two stage operation.

There are rare instances where Cushing's disease has been assigned to an adrenal-like tumor of the ovary, a pituitary adenoma large enough to cause enlargement of the sella, or a tumor in the region of the thymus. In one of the author's cases, no adrenal tumor was demonstrated by x-ray, and following x-ray therapy to the pituitary, pain developed in the patient's abdomen A mass was then palpated practically in the midline of the abdomen. Exploration revealed a large tumor in the body of the pancreas which on pathologic examination was described as malignant pheochromocytoma with numerous scattered islands of adrenal cortical-like cells. After

the removal of this tumor the patient resumed menstruation, lost the contour of Cushing's disease and became pregnant. The pregnancy was successful, with a normal child being delivered. However, because of atony of the uterus, the patient went into shock from hemorrhage and multiple transfusions were necessary. Following delivery of the child the patient was unable to breast feed the infant, her periods did not return, and some months later she presented a picture of pituitary insufficiency or Sheehan's disease. Sheehan first described pituitary cachexia following childbirth and showed that it was due to infarction of the pituitary arteries from shock and blood loss. We feel convinced that 4,000 roentgen tumor units to the pituitary was not responsible for the pituitary insufficiency, first, because the patient menstruated again and went through pregnancy and, second, the same dose has been applied to others without such consequences. As a matter of fact, it has been shown, I believe, that as much as 12,000 r tumor dose units has been given to the pituitary in patients who have cancer without showing any alteration in the structure of the normal pituitary gland as determined at postmortem examination.

The results to be expected from the successful treatment of Cushing's disease are generally satisfactory. There is loss of roundness of the face; there may or may not be some loss of excess hair. Acne, if present, will clear up. The total red blood count will decrease, the differential count return to normal and the eosinophils will rise. If the diabetes is mild, it will be completely taken care

of. If it is a severe diabetes and if a total adrenalectomy is done, there may be practically no need for insulin.

The hypertension may be decreased, although if there has been severe hypertension with high diastolic pressures, a return to normal blood pressure will probably not occur. Increased strength will come about; there may be loss of weight without any attempt to diet. Menstruation may return and pregnancy is possible. However, in some cases in which there is presumably atrophy of the ovaries, normal menstrual periods may not ensue. In males there may be return of sexual desire with or without fertility. The author does not know of any male patient among his cases who has been definitely known to be fertile.

X-ray studies have shown deposition of calcium in the osteoporotic bones over a period of some years.

Previously, testosterone was administered in fairly large doses in Cushing's disease because of the generalized muscular weakness and because of its anabolic effect. I have not been impressed with the use of testosterone except in one patient who was treated elsewhere over a period of several years with large doses of testosterone with a complete remission. Whether this was due to testosterone or a spontaneous remission is difficult to say. As stated previously, it may be said that results of treatment are satisfactory; if roentgen therapy is attempted and fails, adrenalectomy can be performed. In our series, failure of partial adrenalectomy in one case was treated successfully with roentgen therapy.

ADDISON'S DISEASE

Addison's disease is often due to tuberculosis of the adrenal glands or may be due to primary cortical atrophy. Whether primary cortical atrophy is the result of a defect in the secretion of corticotropin from the pituitary gland is unknown. It is well to remember that the adrenal insufficiency associated with panhypopituitarism does not often resemble that of Addison's disease.

The symptoms of Addison's disease are usually well known, namely, pigmentation of the skin, loss of weight, anorexia, often diarrhea, weakness, hypotension, some anemia, or there may be just black freckles and pigmentation of the mucous membranes or of the areas of friction, such as the elbows, the knees or even around the anus. When the adrenal glands are deficient due to hypopituitarism, pigmentation does not occur and there are not the usual manifestations of salt loss as seen in Addison's disease.

For every case of Addison's disease discovered, there will be 8 or 10 other patients for consideration with hypotension, anorexia and weight loss who do not have this disease.

The patient with Addison's disease is usually sick, whereas the neurasthenic patient has not gone through the weakness, diarrhea, weight loss and severe anorexia that the patient with Addison's disease goes through, especially during periods of stress. If the diagnosis cannot

be made clinically, which can be done in most instances, then certain tests may be carried out which will be of help in the diagnosis.

From the clinical point of view, the water test is perhaps the most efficient in excluding frank Addison's disease. This test known as the Wilder-Kepler water test consists of ingesting a large amount of water in the morning on a fasting stomach. Formerly it was thought that the night volume of urine should be determined, but now if 1,000 cc. of water is ingested in the morning without breakfast, the excretion of water following this ingestion determines whether or not there is adrenal insufficiency. If the patient excretes over 800 cc. of water after the ingestion of 1,000 cc. it is almost certain that there is no adrenal insufficiency. If, on the other hand, the amount excreted is less than 800 cc., there is a possibility.

Or, if 3 ounces of tap or warm water is taken for each ten pounds of body weight during a period of about twenty minutes under fasting conditions and not over 100 cc of urine is excreted each hour for four hours, the test may be considered positive. There are various ways of carrying out this test, but the main indication for adrenal insufficiency is the poor excretion of water over a four hour period following ingestion of approximately 1,000 cc. of water. If during the first or second hour there is excretion of over 100 cc, it is not likely that Addison's disease is present. This test can be carried out at home and is particularly significant if there is a normal diuresis following the ingestion of this amount of

water, as regards ruling out Addison's disease. If, however, the test is positive, it does not make a definite diagnosis of adrenal insufficiency since the test may be positive in sprue, possibly in anorexia nervosa, pituitary insufficiency, occasionally in hyperthyroidism, and occasionally in liver disease or any debilitating disease, as hepatic cirrhosis, renal disease, or rheumatoid arthritis.

If a decision cannot be made on clinical findings and the water test, then the corticotropin (ACTH) test of Thorn may be carried out. This test is relatively simple; 25 units of ACTH are injected intramuscularly. The total eosinophil count is taken before the injection of ACTH and four hours later. If there is a 50 per cent reduction in the total eosinophil count, then it is probable that the adrenal cortices are normal and respond to stimulation. Since there is a gradual fall in the eosinophils during the morning hours, the test should preferably be carried on in the afternoon, omitting lunch.

There are several limitations to this test; first, the unreliability of the average technician in counting the total eosinophils and, second, the possibility of a varying potency of the corticotropin preparation.

A more effective technique consists of giving 40 to 80 units of ACTH gel daily for two days, and determining the excretion of 17-ketosteroids or corticoids in the twenty-four hour urine. A prompt rise in these steroids indicates that the adrenal cortex is responsive to stimulation and therefore that the adrenal cortex is not de-

stroyed by tuberculosis or primary cortical atrophy. The adrenocortical response should also decrease the total eosinophils to practically zero. If 20 units of corticotropin or ACTH are given intravenously, with 500 cc. of saline over an eight hour period daily for two days, the eosinophil count should also decrease to zero. With this there is a corresponding increase in corticoids of the urine. Twenty-four urine specimens should be collected for one or two days before the administration of ACTH to determine the output of 17-ketosteroids as well as the corticoids. In panhypopituitarism several days of stimulation may be necessary to evoke a response.

The diagnosis of relative adrenocortical insufficiency as determined by carrying out various highly technical procedures is still open to question as a sound clinical procedure. The author believes that a patient either has adrenocortical insufficiency which is sufficient to cause clinical symptoms or that he does not have such. It is the opinion also of the author that Addison's disease can usually be diagnosed clinically and that the tests carried out are usually of confirmatory nature and do not actually make the diagnosis. As in all situations, there are undoubtedly cases where the employment of these tests is helpful but it is doubtful if a great many new cases of adrenocortical insufficiency have been uncovered by the employment of these tests. However, in doubtful cases and where facilities are available, the patient should be given the benefit of such investigation.

Treatment

The treatment of Addison's disease depends on whether or not the patient is in an acute situation or whether it is a chronic one. For immediate effects in chronic cases, the administration of cortisone orally in doses of 50 mg. a day should greatly improve any patient with Addison's disease. Some physicians are using only cortisone but it is safe to implant one or two pellets of desoxycorticosterone and administer 12.5 to 25 mg. of cortisone daily, partly because patients who have been treated with desoxycorticosterone alone may die, which is probably due to hypoglycemia from the lack of sugar type of hormone. Therefore the combined use of desoxycorticosterone acetate and cortisone is the preferred treatment.

The administration of testosterone in the form of testosterone propionate two or three times a week in doses of 50 mg. each, or in the use of depo-testosterone or testosterone cyclopropionate in doses of 100 mg. every ten days to two weeks, produces certain anabolic effects which may be helpful in the treatment of Addison's disease. However, such treatment is rarely used now in view of the adequacy of the treatment with desoxycorticosterone acetate pellets and the use of cortisone orally. Desoxycorticosterone acetate may be used in buccal tablets which are absorbed through the mucous membranes; this may be a satisfactory form of treatment but, practically, the implantation of pellets is effective and relieves the patient from the daily bother of buccal therapy.

PHEOCHROMOCYTOMA CAUSING PAROXYSMAL OR SUSTAINED HYPERTENSION

A pheochromocytoma is a tumor of the chromaffin tissue of the adrenal medulla. It is usually benign, although it may be malignant—usually of mild degree. Due to the fact that chromaffin tissue exists elsewhere in the body, a pheochromocytoma may be found in other places. Several have been recovered about the trachea, a few in the testes and ovaries, some along the aorta as far down as the bifurcation or below, and more often in and about the kidney and adrenal, detached from the adrenal gland.

This disease is one predominantly of females and may occur any time from 2 to 80 years and most frequently between 20 and 50 years. There is nothing unusual about the appearance of the patient with a pheochromocytoma but in one or two instances there may be associated excess of adrenocortical activity as mentioned in the preceding chapter or when the pheochromocytoma develops in the medulla of the adrenal gland it may in some way, as yet unknown, stimulate the adrenal cortex, and thus produce slight cushingoid or adrenogenital signs.

This tumor may cause paroxysmal or sustained hypertension. The reason for hypertension is the excessive secretion of either epinephrine or norepinephrine. If the attacks are paroxysmal it is obvious that there are sudden discharges of these hormones, causing a great rise in blood

pressure with associated symptoms, or there may be sustained hypertension without a history of paroxysmal attacks.

The frequency of paroxysms varies considerably. Patients may go years without one or they may occur weekly. The paroxysm may last only a few minutes, or as long as sixteen hours.

There is no way to suspect a pheochromocytoma in cases of sustained hypertension except to consider it in every patient with hypertension.

Symptoms

In a paroxysm of hypertension there may be throbbing in the body and in the head and at one time or other, severe pounding headache. There is usually excessive sweating, and flushing of the face with circumoral pallor. In older individuals there may be actual substernal distress and orthopnea and, as I have seen, actual hemoptysis during such a spell. There often is great anxiety and fear during one of these episodes and the patient may feel certain that he is going to die. The blood pressure may go to extremely high heights, often with a marked elevation of diastolic pressure and there may be a gallop rhythm of the heart.

In addition to the flushing and the circumoral pallor, there may be a purplish-like blotching of the skin, or there may be cyanosis in extreme situations, and the face as well as the extremities may be cold.

When the patient tells his story of these attacks, he

may state that they might come on during sleep, or as a result of some painful experience, occasionally on some sudden exertion or emotion, sometimes from sneezing or coughing, and other times from turning from a lying position to one side or from leaning forward or backward. They have been known to occur during labor, during the menstrual period, and sometimes during surgery, or with pressure on the abdomen.

The subjective sensations which the patient feels during the paroxysm may be rather difficult for him to describe and might be considered on taking his history to be purely functional, especially because of the anxiety present during the episode. Such sensations as sinking feeling in the stomach, dizziness or choking may be complained of and, as mentioned before, a pounding or expanding headache along with shortness if breath. Hyperventilation with actual tetany or overbreathing may take place and as I noted before, cough and hemoptysis. Some have noted chest pain, or epigastric pain. Nausea, vomiting, or excess salivation may take place. Diarrhea has been noted. Tremor, cramps of the legs, noises in the ear have been described. Following the attack, the patient may feel quite well, or he may have extreme lassitude, weakness, or even prostration.

In patients who have persistent hypertension from these tumors, as in any other patient with hypertension, acute and serious events may occur such as cerebrovascular accidents or renal failure, angina of effort, pulmonary edema or angina decubitus. These might be accepted

as the natural consequences of hypertension, without thought of the real nature of the disorder.

Toxemia of Pregnancy

Hypertension associated with toxemia of pregnancy may be due to pheochromocytoma, the author having seen 2 such patients in whom at a later date pheochromocytoma was discovered. In one instance there was so much retinitis that the patient was practically blind.

Clinical Manifestation

The clinical manifestations may depend somewhat on which hormone is secreted predominantly. Norepinephrine has a greater tendency to raise the diastolic pressure than epinephrine. Norepinephrine will raise the blood pressure without an increase in pulse rate, whereas epinephrine is more likely to cause an increase in pulse rate and not such a high diastolic pressure.

Of interest is the association of diabetic-like states or actual clinical diabetes in pheochromocytoma. In most instances in verified cases the patient either shows a diabetic type of glucose tolerance curve or actually has glycosuria and persistently high blood sugars. Removal of the tumor may be expected to ameliorate the diabetes, if not completely cure it.

Another feature of pheochromocytoma is the tendency for the basal metabolic rate to be elevated, which is more likely the result of excess circulating epinephrine rather

than norepinephrine. Basal rates as high as plus 50 per cent may be found without clinical evidence of hyperthyroidism. We have seen one patient who had hypermetabolism for some years, beginning at the age of 18. There was no enlargement of the thyroid, but finally somewhere a subtotal thyroidectomy was done without relief. The patient developed toxemia of pregnancy and had to be aborted. Because of the persistently high metabolic rate when first observed by our group, a metabolism test was performed under pentothal anesthesia but it still remained elevated. In this case the blood pressure averaged only 150 mm. mercury systolic and 100 mm. mercury diastolic and rarely went over this level. Since there was no evidence of hyperthyroidism or enlargement of the thyroid remnants, further investigation was made for the question of pheochromocytoma. Multiple calcified tumors were noted in the abdomen, exploration was carried out, and three distinct pheochromocytomas loosely attached to each other but not in the actual adrenal glands were found and removed. Within twelve minutes after closure of the incision, the metabolic rate was determined and it was plus 12 per cent, and in a week found to be normal. The blood pressure returned to normal.

This patient reported by Bartels and Arnold subsequently died of coronary thrombosis at the age of 33, a most unusual circumstance at this age. The possible relation of excessive epinephrine secretion over a period of time in individuals who develop coronary disease is thus suggested.

Diagnosis by Special Tests

The diagnosis of pheochromocytoma is often difficult. There are certain compounds which neutralize circulating epinephrine and norepinephrine and are commonly used now as tests for pheochromocytoma. Regitine is the preparation of choice at the present time and should be administered intravenously to patients suspected of pheochromocytoma who have serious and sustained hypertension.

The following steps comprise the procedure for giving the regitine test:

(1) Determine basal resting blood pressure
(2) Give 1 cc. of regitine intravenously
(3) Record the blood pressure every two minutes for twenty minutes
(4) Determine the presence of postural hypotension at the end of the twenty minutes
(5) If there is a significant drop in the blood pressure, continue the test with readings every ten minutes until the blood pressure returns to the basal level, even if it takes two or three hours, to insure the patient's safety

The antidote for this test is epinephrine.

It has been found that there may be false positive tests upon the use of regitine or other anti-epinephrine agents. There may be a fall in pressure without a pheochromocytoma being subsequently found at operation. The reverse

is also true; the patient may have a pheochromocytoma without a fall in pressure on the use of these preparations. False reactions may occur in approximately 10 per cent of patients tested.

There are certain drugs by which paroxysms of hypertension due to pheochromocytoma may be induced. Mecholyl, or histamine, may precipitate a paroxysm. False positive tests with any of these agents may also be evoked, but if the patient is given regitine just before these tests are attempted it will prevent the incitement of paroxysmal hypertension if due to pheochromocytoma. The mecholyl test, which should not be used on patients with a history of asthma or angina pectoris, is given in the following manner:

(1) With the patient in the supine position, record the basal blood pressure.
(2) Give 10 mg. of mecholyl subcutaneously.
(3) Take the blood pressure every minute for at least twenty minutes after the injection.
(4) Record the blood pressure with clinical symptoms, especially anginal pain. Atropine sulfate, gr. 1/100 in intravenous preparation should be on hand for use as an antidote.

For the histamine test use histamine acid phosphate, 2.75 mg., or histamine hydrochloride, 1 cc. Dilute 1 cc. in 9 cc. of water and use 0 5 cc. (or 0.05 histamine base) in intravenous preparation. The procedure is the same as that for the mecholyl test. Following the injection there

may be a temporary fall in blood pressure, after which there is a marked rise in blood pressure if a pheochromocytoma is present. Dioxobenzane and dibenamine are two anti-epinephrine compounds and may be used in place of regitine. All these preparations are to be injected intravenously at a slow rate.

The cold pressor test also may instigate a rise in blood pressure and this is done as follows:

(1) The patient should rest twenty minutes without sedation.
(2) Blood pressure is taken every five minutes until a constant level is reached.
(3) One hand is immersed in ice water to above the wrist and blood pressure is taken in the arm at 30, 60 and every 120 seconds until the highest level is obtained. In pheochromocytoma there may be a marked hypertensive effect or it may not go up at all.

Newer methods of detecting norepinephrine or epinephrine-like substances in the urine have been developed by Goldenberg and others and while the technique is cumbersome and probably not too accurate, at least it can detect excesses of these compounds in the urine. It has been shown by these authors that even in patients with paroxysmal hypertension there may be continued excretion of these substances in the urine in excess between paroxysms. Their methods may not be refined enough to recognize a small per cent of patients with pheochromo-

cytoma, but in every case in which they have been able to demonstrate an excess of these hormones in the urine there has been found a pheochromocytoma at exploration.

Indications for Tests

The question has often arisen whether it is feasible to administer regitine to every patient with hypertension. Several reports have appeared in which several hundreds of patients with hypertension have been given this substance routinely without uncovering a single case of pheochromocytoma.

It would seem justifiable to carry out the regitine test in cases where there has been a history of hypertensive episodes or crises, or in cases where marked fluctuations have been observed. Recent hypertension in a known normotensive person deserves investigation. Unexplained high basal metabolic rates with hypertension also should be an indication for these tests and, as previously mentioned, diabetes and hypertension should make one consider pheochromocytoma

One of the reasons advanced for the failure of regitine to work in some cases of pheochromocytoma where there is considerable renal damage is said to be a decreased excretion of these hormones and the piling up of these hormones in the blood which is so great that the recommended dose of regitine is not sufficient to neutralize them, and thus not lower the pressure.

In a recent patient with paroxysmal hypertension

which reacted well to regitine, and in whom no tumor could be demonstrated by air study, exploration showed a ridgelike prominence of one adrenal cortex which when manipulated during the operation caused hypertension, and which when excised showed pheochromocytoma cells which were not encapsulated in the manner of a tumor. Complete relief to date was obtained by removing this bump or prominence of the adrenal cortex.

Treatment

The treatment of pheochromocytoma is surgical removal. During the operation the patient should be connected to an intravenous set-up and regitine should be injected into the tube to counteract the severe hypertensive episode that may occur during manipulation or removal of the tumor. This should be done carefully, quickly and expertly. Following the removal of the tumor there may be a marked collapse, either from removal of the tumor or possibly from too much regitine, in which case there should be available norepinephrine in solution, and this should be run in at the rate of 0.2 micrograms per Kg. of body weight per minute until the blood pressure returns to normal levels and then the rate of infusion should be decreased to keep it at a normal level. Many deaths have occurred during operations for pheochromocytoma and the mortality previous to anti-epinephrine compounds was probably as high as 15 per cent.

The tumor may not be in the adrenal areas so that a thorough exploration of the abdomen is advisable in

case one is not found there. We have recently seen a young man in whom a pheochromocytoma was removed but who in a few days had a recurrence of all his signs and symptoms so that there must be another pheochromocytoma present, although none was located at the time. Later, at postmortem, a metastatic pheochromocytoma was found in the brain.

It is perhaps worth while to point out here that in the study of cases of hypertension, not only should pheochromocytoma be thought of but also coarctation of the aorta. This is easily suspected if every patient with hypertension had an examination for pulsation of femoral arteries. If these are absent, then neither pheochromocytoma nor ordinary hypertension exists and the probability is that the patient has coarctation of the aorta as can be demonstrated by roentgenograms of the chest showing notching of the ribs which occurs in practically 98 per cent of all cases. In these cases, pulsation of the intercostal arteries can be felt with the fingers along the rib margins There may be a systolic murmur over the aortic area and through to the back or farther down in the chest, and special arterial studies will demonstrate the area of the coarctation. The author mentions this because of the highly satisfactory results of surgery of coarctation in the last ten years.

CHAPTER VI

HYPERINSULINISM

Hyperinsulinism, meaning an excessive secretion of insulin, causes symptoms because of hypoglycemia. Hyperinsulinism, however, is not the only cause of hypoglycemia.

There are a number of factors which maintain the normal level of blood sugar. In Addison's disease or panhypopituitarism, for example, the adrenocortical secretion is reduced or absent. Of these, the cortisone type secretions assist in liver glycogen storage, from which blood sugar is replenished when the patient is fasting or when excessive sugar is used during exercise. If the glycogen of the liver is depleted, insulin continues to act, lowering the blood sugar to levels causing the usual signs and symptoms of hypoglycemia.

In severe liver disease in which there is an inability to store glycogen, there may be hypoglycemia. Conversely, in von Gierke's disease of children, which is essentially an enzymic condition in which glycogen cannot be re-

leased from the liver, hypoglycemia may also occur. It is possible that an extremely low renal threshold for sugar may occasionally be responsible for hypoglycemia.

In infants or children without physical abnormality, spontaneous hypoglycemia may occur and is referred to as idiopathic hypoglycemia. There is a tendency for this condition to be familial. Until recently no definite reason could be assigned as the cause of this disorder. For many years it has been known that there was a substance in extracts of the pancreas which caused hyperglycemia This substance is actually present in a good many commercial insulins. Shortly after the injection of insulin, there may be found a slight elevation of blood sugar during the first half hour. This is not particularly noticeable if insulin is given subcutaneously and probably not much more noticeable if given intravenously, unless possibly in very large doses. It is especially effective in animals when insulin is injected into the portal vein, causing the release of sugar from the liver into the blood stream. There is evidence suggesting that this is a hormone of the alpha cells of the pancreas, which helps to regulate the level of the blood sugar. It is called glucagon, or HGF (hyperglycemic glycolytic factor). Insulin itself is derived from the beta cells. McQuarrie has stated that in 2 cases of idiopathic hypoglycemia in children in which the pancreas was resected with temporary benefit, histologic study revealed an absence of alpha cells. This theory of the cause of idiopathic hypoglycemia in children certainly is attractive, but not yet definitely proven.

Functional hypoglycemia is a term applied to rather mild symptoms without neurological manifestations and, of course, never coma. It is apparently not due to excessive insulin secretion. The mechanism of this type of disturbance is not definitely known but usually occurs in the nervous or vagotonic type of person. The blood sugar may be low but rarely if ever below 60 mg., and there is usually spontaneous recovery. One of the characteristics of this functional type is that hypoglycemia is unlikely to occur early in the morning or after a long fast of twelve hours or so, but may be provoked by eating, particularly high carbohydrate food, with the hypoglycemic manifestations occurring two or three hours later.

ISLET CELL TUMORS AND HYPOGLYCEMIA

Tumors of the pancreatic islets capable of secreting insulin may be benign or malignant. They may be found not only in the body of the pancreas but in aberrant pancreatic tissue. Metastasis of malignant islet cell tumors may be found in the liver. The occurrence of pancreatic islet cell tumors causing hypogylcemia is quite rare. Apparently all ages can be affected and evidence to date suggests that it occurs more frequently in males than in females.

The hypoglycemic state caused by these tumors is usually paroxysmal, may occur frequently, depending on food intake, or may occur at relatively great intervals.

The symptoms of hypoglycemia before reaching the

stage of coma are a feeling of drowsiness, yawning, or an anxious facial expression. The patient may become excited or appear to be under the influence of alcohol. There may be disorientation, aphasia, hallucinations.

The patient may gradually be unresponsive and go into deep coma. Color usually remains good at first; later pallor may develop. There may be various minor neurological signs indistinguishable from some central nervous system disorders, such as temporary monoplegia or hemiplegia. Convulsive seizures, tonic in type, may occur, either unilaterally or bilaterally.

An early symptom may be blurring of vision and an inability to focus the eyes, and perspiration. On the other hand, the patient may be precipitated into a maniacal or abnormal mental state without having been conscious of any warning signs. Fortunately, a good many persons who take insulin and some of those who have tumors causing excessive insulin secretion do have sufficient warning to take sugar in some form to prevent or ward off the attack. The duration of the attack may vary from a few minutes to several hours, depending on the degree and the duration of the hypoglycemia.

Usually but not always there is definite correlation between the level of the blood sugar and the intensity of the attacks, but in rare instances blood sugars have been found below 50 mg. for considerable duration before clinical signs or symptoms develop.

The late consequences of frequent hypoglycemic attacks, particularly in children, may lead to permanent

central nervous system damage. There may be residual sensory, motor and psychic changes, even to complete idiocy. Retardation of growth and actual dwarfism have been observed from repeated attacks in children.

Diagnosis

It is not uncommon for many persons to feel somewhat weak and fatigued and perhaps a little shaky around 11 to 12 o'clock in the morning after an early breakfast. If blood sugars are taken at these times, the physician will be disappointed to find that it is very unusual for blood sugar to be below 80 to 100 mg. In our experience, most patients diagnosed as having hypoglycemic attacks or a hypoglycemic condition do not show hypoglycemia when adequately fasted.

The diagnosis is usually made by finding a blood sugar of 50 mg. or less. Certainly, during the attack, values should be below 50 mg. Fasting blood sugars of this level or below, even without manifestations of hypoglycemia, make one suspicious of an organic cause, especially in an individual who describes the symptoms mentioned previously.

Usually when a six hour glucose tolerance test is done, hypoglycemia may occur at the five or six hour period, but in our experience the fasting blood sugar is usually below 50 mg in the cases in which pancreatic tumors have been found. It is to be remembered that sooner or later hypoglycemia tends to invoke a responsive rise in blood sugar. This may be absent in hypopituitar-

ism, in Addison's disease and possibly in epilepsy, so that these should be differentiated from patients with pancreatic tumor.

Hypoglycemic unresponsiveness can be tested by the intravenous injection of 5 units of insulin after twelve hours of fasting. Blood sugar taken two hours later remains low and does not rise later as in normals. This test rarely needs to be resorted to, as clinical evidence of Addison's disease or hypopituitarism is usually sufficient to differentiate them from patients with islet cell tumor. This test should be avoided if there is suspicion of Addison's disease or, if it is used, intravenous glucose should be available in case the patient goes into a hypoglycemic state.

Treatment

The management of functional hypoglycemia is chiefly one of giving a high protein, moderately high fat diet with minimal carbohydrates and, if necessary, milk between meals. This type of diet can also be used in patients who have hypoglycemia due to an organic cause, particularly pancreatic tumor. Patients have often learned to feed themselves frequently and thus avoid attacks, but as a result may gain considerable weight. The excess carbohydrate which gives them more immediate relief tends to stimulate the pancreas to produce more insulin. Thus the high protein type of diet not only avoids this stimulation but also prevents excessive weight gain.

If it has been definitely established that the blood sugar

is below 50 mg. during an attack or that the fasting blood sugar is persistently below 50 mg., then the patient is a candidate for surgery, except infants or young children. With a history of hypoglycemic attacks, one should not advise surgery unless repeated blood sugars are below 50 mg., thus avoiding unnecessary operation due to possible laboratory errors.

In exploring the pancreas, single or multiple tumors may be found. In the past, tumors have been overlooked due to their small size or their location, in the head of the pancreas or in aberrant locations. When this occurred, four-fifths of the pancreas was often removed. On re-exploration, because of continued attacks, a tumor was often found. According to some, there is only about a 60 per cent chance of finding an adenoma of the pancreas on first exploration.

In exceptional cases where all methods to control hypoglycemic attacks have failed, including exploration and subtotal resection, the possibility of total or subtotal pancreatectomy might be considered in view of the fact that the diabetes is comparatively mild in relation to clinical cases of diabetes. Total pancreatectomy, however, is to be avoided on account of the loss of pancreatic juices. In this connection, one of the reasons for the relative mildness of diabetes on removal of the pancreas may be the loss of the hyperglycemic factor from the alpha cells as well as the insulin from the beta cells.

In infants or young children, attacks can be prevented by the use of corticotropin in gel. Even in adults awaiting

surgery or in whom the latter might be contraindicated for one reason or another, corticotropin in gel may be used to prevent attacks. Dosage depends on age and severity; in infants or children, 5 units daily or every other day may be tried, whereas in adults, 10 mg. or more may be an adequate dose. Cortisone may be tried. Apparently at some later date (to be found by trial and error), corticotropin may be discontinued in children with the idiopathic type of hypoglycemia.

Before contemplating removal of any of the pancreas in a case where a pancreatic adenoma is not found, one should consider or should have thought of the possibility of factitious hyperinsulinism. Nurses, or others who are familiar with insulin and the use of hypodermic syringes, are the ones to be most suspicious of should an adenoma be suspected Several very interesting cases of hypoglycemia in which multiple operations have been done, but in which the real cause was self-administration of insulin, have been reported, or at least related in medical circles.

HYPERGLYCEMIA

Diabetes mellitus is not presented in this book. Hyperglycemia may be caused by other endocrine disorders. The question as to whether a latent diabetes mellitus exists when hyperglycemia occurs is not the point of the present discussion.

Hyperglycemia and glycosuria are prima-facie evidence clinically of diabetes mellitus. The author only wishes to

point out certain endocrine disorders which cause hyperglycemia, or aggravate or make manifest latent diabetes. These are discussed in appropriate chapters, namely:

Acromegaly
Hyperthyroidism
Cushing's Disease
Pheochromocytoma

CHAPTER VII

GONADS

OVARIES

The most frequent endocrine disturbance in women is abnormal menstruation. This includes excessive bleeding, amenorrhea, irregularity or oligomenorrhea, polymenorrhea or too frequent menstrual periods, the late appearance of the menarche, the premature cessation of menstruation, as well as dysmenorrhea.

The term primary amenorrhea refers to amenorrhea which has always been present, whereas primary hypogonadism indicates ovarian deficiency which has always existed. Primary amenorrhea may not always be associated with decrease or absence of secondary sexual characteristics, but may be due solely to congenital absence of the uterus or unruptured hymen, i e., hematocolpometra, in which case it is obviously not an endocrine disorder.

Secondary amenorrhea indicates that normal menstrual periods have occurred in the past, whereas secondary hypogonadism implies previous normality and that the ovaries are deficient either through failure of pituitary gonadotropin secretion or some other disorder which may

suppress ovarian function. These terms are used largely for descriptive purposes and do not have too much importance in clinical practice.

NORMAL MENSTRUATION

Menstruation is the result of a complex hormonal play upon the endometrium of the uterus. Briefly stated, the primary follicles of the ovary are stimulated by the follicular stimulating hormone (FSH) of the anterior pituitary, all other things being equal. In the average twenty-eight day cycle the follicle develops and the ovum contained therein is extruded on or about the fourteenth day. The cause of the phenomenon of ovulation may be the effect of luteinizing hormone (LH) of the anterior pituitary. At the time of ovulation there is a definite change in the body temperature and often there may be pain as well as spotting, frequently referred to as "mittelschmerz." The temperature taken before rising in the morning will show a drop perhaps of one half or a whole degree at the time of ovulation, and the following day there is a rise in the temperature of 0.6 degree F. and this is maintained until just before menstruation.

Following ovulation the follicle then becomes known as the white body or corpus luteum, which is solid tissue. The function of the corpus luteum is to secrete progesterone (and probably estrin), which has a definite effect on the uterine mucosa. The existence of a third anterior pituitary hormone which maintains the corpus luteum

as a functioning unit to the time of menstruation is not well proven. It is described as the corpus luteum sustaining or luteotropic hormone (LT).

As the follicle develops in the first part of the menstrual cycle, estrogen is secreted and the nature of this estrogen is in all probability estradiol. This produces chiefly a proliferation of the endometrium. It is distinctly possible that when the secretion of estrogen by the follicle is at its maximum, it suppresses the production of follicular stimulating hormone (FSH) in the anterior pituitary and at the same time stimulates the secretion of luteinizing hormone (LH) from the anterior pituitary; or, since progesterone may well be excreted by the ovary before actual ovulation, the latter may be the stimulus to luteinizing hormone. When progesterone is at its maximum secretion, it may, as is thought to occur in many instances, actually suppress the contained secretion of luteinizing hormone of the pituitary or even suppress the theoretical luteotropic hormone, thus stopping the secretion of progesterone. With the deterioration of the corpus luteum at this point, the endometrial lining which has been further built up to the progestational type of endometrium breaks down and menstruation follows.

It is hypothesized, too, that the hypothalamus in some way has some influence over the anterior pituitary in the normal course of events in the menstrual cycle.

It can therefore be seen that ovulation cannot occur without proper development of the follicle. It is also obvious that without ovulation a progestational endometrium

is not produced; thus pregnancy cannot take place, first because there is no ovum or secondly, because the progestational endometrium is necessary for nidation of the ovum.

However, menstrual bleeding may occur without ovulation due to cyclic stimulation of the follicle by follicular stimulating hormone of the anterior pituitary. When estrogen has been secreted by the follicle in sufficient amounts it in turn suppresses the elaboration of follicular stimulating hormone of the anterior pituitary. Ultimately this causes the follicle to secrete less estrogen so that the effect on the endometrium is withdrawn, causing withdrawal bleeding similar to that following administration of estrogens to the amenorrheic or menopausal female. It is thought that at the beginning of menstruation or menarche the cycles are anovulatory in many instances.

This is important to remember, not only in young girls but especially in some females who menstruate regularly yet are unable to conceive.

VARIATIONS OF NORMAL MENSTRUATION

What are the limits of normality in regard to the duration, the amount of flow, the regularity of menstrual periods in the normal female? A famous Viennese gynecologist is said to have commented that the only regular thing about a woman's periods was their irregularity. The average age of onset of the menarche is from 12 to 14 years,

with a range of normal menarche from 9 to 18 years of age. The duration of normal menstrual cycle varies from 21 to 65 days, the majority averaging approximately 28 days. Extremes should be viewed with suspicion unless the same pattern has been present since menarche. Although many women feel that their menstrual periods are regular, the variation in the duration of the cycle not infrequently is from one to nine days. The duration of normal menstrual periods may be from one to seven days with 90 per cent averaging between three to six days. The average number of napkins used per period ranges from two to thirty, with the majority averaging two to eight per day. It is obvious that thirty napkins per day is excessive, but the number used may depend on the frequency with which they may be changed by the individual person.

Approximately 48 per cent of normal women may pass clots during menstruation. The average amount of hemoglobin lost during a menstrual period is from 11 to 42 mg. This is from 1 to 20 ounces of blood. Thus it can be seen that the range of normal menstruation is wide and attempts to normalize the periods may be entirely unsuccessful unless some definite disturbance can be discovered, and these were mentioned in a previous chapter.

In regard to ovulation, it is believed that ten to fourteen days after the onset of menstruation is the usual time in women having cycles of from 24 to 34 days. In a small minority, ovulation may take place as soon as eight days after the onset of menstruation

PREMENSTRUAL MOLIMINA

Many women have no premenstrual phenomena whatsoever but many others have discomfort which may or may not be intensified by the patient's threshold of pain. The question always arises, what can be considered a normal amount of premenstrual discomfort and what is abnormal.

The common premenstrual phenomena or symptoms are changes in the psyche which are manifested by nervousness, emotional outbursts, restlessness, sometimes high spirits but more frequently depression. Some women may actually become psychotic during the premenstrual phase. During the premenstrual cycle women may have aggravations of seborrheic dermatitis, ulcerative stomatitis, or erythema multiforme. Women subject to migraine may have typical migraine headaches at this time, or headaches not characteristic of migraine. There is often a considerable feeling of lassitude along with a feeling of bloating and sometimes noticeable swelling of the hands, feet, and even eyes and face. Frequency of urination may occur. There may be some aching of the breasts.

DYSMENORRHEA

Pelvic discomfort is frequently complained of, and back pain with radiation occasionally into the legs. It has been

demonstrated that the bloating sensation may be accompanied by an actual increase in weight from sodium retention.

There may be actual pathologic physiological reasons for this type of disturbance. In some women a menstrual toxin has been demonstrated during this time. Some believe it is similar to necrosin which is a substance obtained from pleural effusions due to irritation by turpentine injections. It may be due to a defective secretion of abnormal progesterone or other unknown causes.

It is not quite fair to believe that all women who have marked premenstrual symptoms are of neurotic disposition. One must not forget that endometriosis may cause considerable premenstrual discomfort, particularly pain, and endometriosis may be present at any time from the age of 12 or 13, so that with a history of dysmenorrhea from the menarche, it does not necessarily point to a psychosomatic disorder.

It can be assumed in any case that the disabling effects of dysmenorrhea are, as in other diseases, the result of a possible pathologic cause and the reaction of the patient to such cause.

EXCESSIVE BLEEDING

There may be excessive bleeding early in menarche, possibly due to the follicle not having secreted sufficient estrogen to inhibit the anterior pituitary and the endo-

metrium may remain in a continuously proliferative state. Should ovulation occur, the natural evolution of the premenstrual endometrium then comes about and normal menstrual flow ensues. During the menarche it is often impossible or undesirable to obtain endometrial biopsies but basal temperature charts may be used to determine the presence or absence of ovulation.

TREATMENT OF EXCESSIVE BLEEDING

The treatment of excessive menstrual bleeding at the menarche from the practical point of view consists first of making sure that there is adequate nutrition. With malnutrition there may possibly be deficient liver function as regards its ability to completely break down circulating estrogens which if not done causes a proliferative endometrium to persist. If this situation exists, every effort may be made to provide the proper nutrition and this should include supplemental vitamins, particularly B complex, as an added insurance of adequate liver function. The value of the latter can only be conjectured, but is based on animal experiments.

If the bleeding is continuous, several practical procedures may be carried out.

(1) Bleeding may be completely suppressed by administration of stilbestrol in doses of 5 to 10 mg. given orally. This, however, is only a temporary measure.

(2) Conjugated estrogens in the form of injectable

premarin can be given intravenously in two or three doses over a twenty-four to thirty-six hour period if hemorrhage is severe, with temporary suppression of excessive flowing.

(3) Testosterone in doses of 50 to 100 mg. daily for three or four days may also suppress excessive bleeding but this should only be used temporarily because of masculinizing effect.

(4) It is undoubtedly wisest to try the use of progesterone. This may be given during the bleeding episode. It can be administered intramuscularly in doses of 10 mg. a day for a period of five to seven days. This should produce a progestational endometrium and a satisfactory sloughing of the endometrium with cessation of menstrual flow in four to five days. It has been shown, however, that anhydrohydroxyprogesterone is readily absorbed from the buccal membranes just as adequately as intramuscular injection. Pure progesterone or anhydrohydroxyprogesterone may be obtained in the form of buccal tablets and can be absorbed when inserted in the mouth between the teeth and the cheek, or under the upper lip, and allowed to dissolve without interfering with talking, eating or drinking. Three to six 10 mg. tablets daily may be given this way over a period of a week for adequate progestational effect.

If excessive flowing then subsides, progesterone given in either manner should be administered on about the twenty-first day of the ensuing cycle and if results are satisfactory this can be continued for a few months and then the medication omitted to see if normal cycles may

occur. It is to be admitted that in some instances none of the hormonal therapies suggested will be necessarily effective. While it is desirable to avoid radical procedures such as x-ray therapy, exploratory laparotomy and/or hysterectomy, in some instances it may become necessary if no pathology is found.

Before such a procedure is contemplated, every effort should be made to rule out disease in the ovaries by rectal or vaginal examination under anesthesia or even culdoscopy if deemed worth while. Uterotubograms are valuable in some cases. It should not be forgotten that certain blood dyscrasias, in which there is a tendency to bleed, may be present and these should be ruled out by the usual laboratory procedures.

The treatment of excessive flowing in the menarche is also used in excessive flowing in adult women. There are, however, other possibilities such as polyps in the endometrium of the uterus, submucous fibroids or endometriomas, shown by uterotubograms, and ovarian cysts or tumors producing constant proliferative effect due to estrogen secretion.

In adult women with excessive flowing when uterine carcinoma or polyps have been excluded by diagnostic dilatation and curettage or other methods of determining malignancy, excessive bleeding may be controlled with testosterone cyclopentylpropionate in doses of 200 mg. every ten days. Stilbestrol in doses of 5 to 25 mg. a day can also be used and kept up more or less indefinitely if the drug is well tolerated and no complications arise,

such as edema, oozing, or recurrent uterine hemorrhage.

In several instances of excessive hemorrhage associated with fibroids seen by the author, in which multiple transfusions did not increase the hemoglobin or red count, cessation of flowing was accomplished by the administration of large doses of stilbestrol up to 50 mg. a day, following which, when hemoglobin was adequately restored by subsequent transfusions, hysterectomy was performed without incident.

For prolonged menstrual periods which do not incapacitate the patient or cause anemia and in which all methods of examination have not demonstrated anything pathological, trial of progesterone previous to the period may be carried out but it is to be admitted that this is not always successful. In such cases the decision as to surgical procedures depends on a great many factors such as the nearness of the menopause and the desirability of further pregnancies. Perhaps it is better not to carry out any extended procedure if the only inconvenience is the duration of the menstrual flow. Sometimes the condition may correct itself with the onset of menopause. When this excessive flowing occurs within the probable time of the menopause it may be a manifestation thereof, the bleeding may be anovulatory, in which case the type of treatment is determined by some of the factors mentioned above, or no treatment is carried out until there is actual cessation of the menses. It is at this time that the use of large doses of stilbestrol or testosterone is more feasible than earlier in the reproductive age.

occur. It is to be admitted that in some instances none of the hormonal therapies suggested will be necessarily effective. While it is desirable to avoid radical procedures such as x-ray therapy, exploratory laparotomy and/or hysterectomy, in some instances it may become necessary if no pathology is found.

Before such a procedure is contemplated, every effort should be made to rule out disease in the ovaries by rectal or vaginal examination under anesthesia or even culdoscopy if deemed worth while. Uterotubograms are valuable in some cases. It should not be forgotten that certain blood dyscrasias, in which there is a tendency to bleed, may be present and these should be ruled out by the usual laboratory procedures.

The treatment of excessive flowing in the menarche is also used in excessive flowing in adult women. There are, however, other possibilities such as polyps in the endometrium of the uterus, submucous fibroids or endometriomas, shown by uterotubograms, and ovarian cysts or tumors producing constant proliferative effect due to estrogen secretion.

In adult women with excessive flowing when uterine carcinoma or polyps have been excluded by diagnostic dilatation and curettage or other methods of determining malignancy, excessive bleeding may be controlled with testosterone cyclopentylpropionate in doses of 200 mg. every ten days. Stilbestrol in doses of 5 to 25 mg. a day can also be used and kept up more or less indefinitely if the drug is well tolerated and no complications arise,

such as edema, oozing, or recurrent uterine hemorrhage.

In several instances of excessive hemorrhage associated with fibroids seen by the author, in which multiple transfusions did not increase the hemoglobin or red count, cessation of flowing was accomplished by the administration of large doses of stilbestrol up to 50 mg. a day, following which, when hemoglobin was adequately restored by subsequent transfusions, hysterectomy was performed without incident.

For prolonged menstrual periods which do not incapacitate the patient or cause anemia and in which all methods of examination have not demonstrated anything pathological, trial of progesterone previous to the period may be carried out but it is to be admitted that this is not always successful. In such cases the decision as to surgical procedures depends on a great many factors such as the nearness of the menopause and the desirability of further pregnancies. Perhaps it is better not to carry out any extended procedure if the only inconvenience is the duration of the menstrual flow. Sometimes the condition may correct itself with the onset of menopause. When this excessive flowing occurs within the probable time of the menopause it may be a manifestation thereof, the bleeding may be anovulatory, in which case the type of treatment is determined by some of the factors mentioned above, or no treatment is carried out until there is actual cessation of the menses. It is at this time that the use of large doses of stilbestrol or testosterone is more feasible than earlier in the reproductive age.

AMENORRHEA

It has been stated that the continuous presence of a proliferative endometrium may cause excessive flowing. On the other hand, amenorrhea may result from continuous proliferative endometrium which does not break down; this can be determined by several office procedures.

One of the most frequent situations encountered is that of a young woman of 18 to 25 years who has become amenorrheic, and on examination appears perfectly well, with normal secondary sex development and, on inquiry, has normal sexual inclinations. This type of amenorrhea is often found in girls who have changed their environment, such as going away to college, or have been through an emotional strain or in some instances no possible etiological factor can be uncovered.

OLIGOMENORRHEA

This phenomenon may be normal in some instances, at least no cause will be demonstrable in most cases. One must consider in oligomenorrhea or amenorrhea the Stein-Leventhal syndrome which is characterized by large, white ovaries due to a thick fibrous capsule. In about half the cases there may be mild hirsutism and occasionally there may be a slight enlargement of the clitoris, but no other masculinizing features. 17-Ketosteroids may be elevated

or normal. Wedge resection may permit ovulation and pregnancy. Cortisone may be tried, 100 to 200 mg. per day.

DIAGNOSIS, USE OF VAGINAL SMEARS AND TREATMENT

In the girl who is under the age of 15 or 16 who has secondary sex development, the presence or absence of a proliferative endometrium can also be judged by vaginal smear preparation. The iodine vapor smear as described by Mack has been useful in the author's hands and is entirely an office procedure. (See chapter on Laboratory.) Unless the hymen is completely intact, a small swab can usually be inserted through the aperture and the vaginal smear obtained. If there is evidence of adequate estrogen effect, it can then be assumed that there is a proliferative endometrium. In such cases the use of progesterone as described above by buccal administration may well produce a normal menstrual flow and this can be repeated for several months in hopes that ovulation may take place. As stated previously, it is entirely possible that progesterone may be the stimulator of luteinizing hormone and hence ovulation.

PITUITARY TUMOR

If the amenorrhea has existed for a period of six months or longer, it is advisable to x-ray the skull because chro-

mophobe pituitary tumors, craniopharyngiomas or chromophile pituitary tumors may be present in 2 or 3 per cent at least. Routine examination of the vaginal smear as mentioned above should be done. Often the vaginal epithelium is fairly well estrinized and will respond to progesterone therapy. In some cases with an enlarged sella where there is no pressure effect, such as visual disturbance or headache, it probably is best to withhold x-ray therapy if the vaginal epithelium is estrinized, using only progesterone (see Hypopituitarism). The author has seen several young women past 25 years of age who have been amenorrheic over three and four years with decidedly large sella turcicas without evidence of local pressure effects, in whom the vaginal smear showed a good estrin effect as well as hormone assays for estrin, and who responded to progesterone regularly and after from four to five months trial continued to have normal menstruation without the use of progesterone. The mechanism of the re-establishment of normal cycles in such cases is, of course, obscure, but the procedure is always worth a trial.

In the patient with amenorrhea and no vaginal estrin effect whatsoever, pituitary tumor should always be suspected. On the other hand, it is not uncommon in cases of anorexia nervosa with extreme malnutrition to find that the vaginal smear may be poorly estrinized. In such cases it is necessary to prescribe estrogens in any form in doses equivalent to about 0.5 to 1 mg. of stilbestrol *daily* for twenty-one days, followed by the buccal administra-

tion or even oral administration of progesterone or progesterone-like compounds for seven to ten days to produce a normal cycle of events and menstrual bleeding. It is also of first importance to feed the patient and if weight gain is adequate, periods may return.

ANOREXIA NERVOSA AND HYPOPITUITARISM

In cases of anorexia nervosa treated by the author, the estrogen-progesterone therapy was successful in some instances; in other cases only slight spotting occurred. This may be due to the fact that the end organs were not responsive, at least the endometrium, but in all instances when estrogen has been given to girls with anorexia nervosa, the vaginal smear has shown a well marked effect of estrogen as determined by the vaginal smear.

It is characteristic that the marked anorexia nervosa of young, unmarried females is characterized by very little disability, even though the patient may be skin and bones. The differentiation between anorexia nervosa and hypopituitarism of primary pituitary origin may be difficult, but it is unlikely that any girl of this age would develop panhypopituitarism without a chromophobe, chromophile pituitary tumor, craniopharyngioma, a history of shock following delivery, or an acute febrile episode with headache. Furthermore, the patient with severe panhypopituitarism is not as malnourished as the average patient with anorexia nervosa but is more incapacitated by her weakness and lack of endurance. Also, if pan-

hypopituitarism were present to a severe degree and of sufficient duration, there would be fairly marked loss of axillary and pubic hair in the majority. One of the surprising things I have noted in anorexia nervosa in spite of amenorrhea and the other findings is occasionally an increased growth of body hair. Rarely in anorexia nervosa is there a change in blood counts and often no decrease in the urinary 17-ketosteroids, or glucocorticoids.

OTHER CAUSES OF AMENORRHEA

Secondary amenorrhea in females can be due to other glandular disturbances such as the onset of adrenogenital syndrome. The characteristics of this disorder are recognized by the excessive hair growth, acne, enlargement of the clitoris, change in voice and loss of normal sexual inclinations. Cushing's disease is another cause of amenorrhea and can be recognized by the physical changes described under Cushing's disease. The Stein-Leventhal syndrome, as mentioned before, may cause amenorrhea or oligomenorrhea.

One must also consider certain tumors such as arrhenoblastoma, which may occur at almost any age, and adrenal-like tumors of the ovary. Amenorrhea is common in myxedema, although there also may be excessive bleeding in myxedema. Hyperthyroidism may be associated with amenorrhea or decreased or scanty periods. One must not overlook, furthermore, the possibility of acro-

megaly in its earliest stages in which the physical changes are barely recognizable except by the physician who considers acromegaly in the differential diagnosis of every case of amenorrhea.

Mention was made previously of the role of the liver in the metabolism of hormones. Failure of the liver to break down the unused estrogen complexes circulating in the blood in women with cirrhosis may cause altered menstrual function from amenorrhea to excessive bleeding.

TREATMENT OF DYSMENORRHEA, INCLUDING ENDOMETRIOSIS

The treatment of dysmenorrhea is at times a very difficult problem. The amount and type of treatment necessary depends on the degree of invalidism that occurs. Certainly every woman with dysmenorrhea has the right to feel that there is something definitely abnormal about it and should not be made to feel that it is entirely mental. Cervical stenosis might be a contributing factor in some.

Endometriosis is the one disease that should be excluded in the dysmenorrheic patient. Examination for endometriosis should be carried out before or during menstruation. Premenstrually, endometrial cysts are most tender. During or after menstruation they may be engorged with blood Endometriosis may implant itself in the uterine wall, in the tubes or ovaries, throughout the pelvis, and it may be found in the sigmoid, rectum, or even in the bladder. Endometriosis can also occasionally

be found in the vaginal wall and it is therefore desirable to examine patients at the menstrual period, at which time the so-called blueberry cyst might be identified. These have also been identified in the bladder. On vaginal examination, masses may be palpated, the uterosacral ligament may be tight, firm and tender, and the uterus enlarged in cases with endometriomas.

Meigs has said that endometriosis is a disease of women who are not having children. He finds it more frequently in private patients as compared to ward patients. A particularly characteristic history is the onset of dysmenorrhea after eight or ten years of pain-free periods in an unmarried woman, or a married woman who has not been pregnant.

The incidence according to age in individuals discovered to have endometriosis is greatest between the age of 34 and 38, with a majority between the age of 29 and 48.

The treatment of dysmenorrhea due to endometriosis is not entirely satisfactory. It has been shown that large doses of stilbestrol will entirely suppress menstruation and ovulation in some cases and that the endometrial cysts will then not become distended. It is believed that in some instances endometriosis may almost entirely disappear while the patient is kept anemorrheic by the use of stilbestrol. Strilbestrol in doses of 5 to 25 mg. per day works exceedingly well in a small percentage of patients. The dyspareunia so frequently associated with endometriosis may entirely disappear. There may be a great sense of well being on taking stilbestrol.

On the other hand, one may get into difficulty with continual or periodic oozing, sometimes excessive bleeding, which may usually be controlled by doubling the dose, but in general it is not wise to continue with stilbestrol if the patient cannot tolerate it, although in some, after several weeks of large doses, the initial nausea may disappear. If excessive bleeding or oozing occurs, it is probably best to stop it. Some physicians give methyltestosterone in doses of 20 to 30 mg. for ten days before the menstrual period, believing that it decreases menstrual pain.

Perhaps the most satisfactory treatment of endometriosis is surgery, consisting of a presacral neurectomy and removal of all ovarian cysts, leaving behind the ovaries and the uterus, particularly in those women who desire to become pregnant. This does not insure pregnancy, but it may occur. It has also been known that women with endometriosis who have been barren may become pregnant during or after a course of four to six months of stilbestrol therapy, showing that ovulation is not inhibited in all cases.

Results of the surgical treatment are fairly satisfactory but as long as the ovaries continue to function there may be a recurrence at a later date. If no further pregnancy is desired, panhysterectomy can be performed or x-ray therapy can be given which will stop ovarian function, following which endometriosis should recede. In some cases of extensive endometriosis, surgery is not possible and it was in such a case that the author first used large doses of stilbestrol with an exceptionally good result. This

patient has continued on stilbestrol for approximately eight years and has been amenorrheic during that time. Dyspareunia prevented intercourse, but this situation has been entirely corrected. As stated before, in extensive endometriosis adhesions may result, causing constriction of the rectum with obstructive symptoms. In one such case, x-ray treatment to the ovaries plus testosterone therapy weekly in doses of 50 mg. over a period of about six months caused a disappearance of the rectal constriction, which probably was not due to fibrous tissue but to actual endometrial implants.

Dysmenorrhea or premenstrual dyspareunia may be caused by endometriosis, even though examination fails to reveal it. Laparotomy is justified at the time of pain if symptoms are really severe.

Various and numerous remedies are used for dysmenorrhea. Aspirin, or aspirin and whiskey, is a favorite home remedy and sufficient aspirin should be used to produce an effect. There are various antispasmodics which may be tried. The author has no distinct preference, although recently Glybrome has been tried with moderately good results.

Cervical stenosis as a cause of dysmenorrhea is always to be considered and can easily be identified and corrected, particularly if dilatation and curettage is to be carried out.

In some instances without demonstrable pathology, presacral nerve dissection has been done with gratifying results. Doyle has been able to carry out this procedure by culdoscopy.

It is generally believed that if ovulation does not take place, dysmenorrhea does not occur. This may be the reason why some women have alternating painful and pain-free periods.

OVARIAN AGENESIS

Ovarian Short Stature Syndrome

Ovarian short stature syndrome is also known by other names, such as ovarian agenesis, Turner's syndrome, or congenitally aplastic ovaries. The ovarian short stature syndrome is characterized by very small ovaries which lack the differentiated elements of the parenchyma. There are many small primary follicles, no mature follicles, and no luteal changes are noted.

The nondevelopment of the ovaries, however, is only part of the entire syndrome. It appears that it is a congenital disorder with other congenital anomalies, the cause of which is unknown.

Turner, in describing this syndrome, pointed out the peculiar physical abnormalities, such as congenital webbing of the neck with a low hairline at the back of the neck, the increased carrying angle of the arms and the limited growth Other congenital abnormalities noted in this syndrome have been coarctation of the aorta, congenital heart disease and other minor defects

They are well nourished, rather stocky, have a few complaints as a rule, and show very little indication of the syndrome until the usual age of puberty other than that

they are shorter than normal. Rarely do these young women ever grow beyond the height of 56 or 57 inches.

If one of these patients is seen before the age of puberty one might well get the impression that they represent a pituitary dwarf since there is little evidence of thyroid or other endocrine disturbance, and very little else on physical examination. The bone age is a few years to four or five years behind the chronological age.

When these patients pass the age of puberty, they then begin to show in the majority of instances a type of urine found only in menopausal women or castrate women, namely, one with a great excess of follicular stimulating hormone. This gonadotropic hormone when elaborated is probably the cause, in part at least, of the phenomenon of puberty. If the ovaries are unable to react, as they are in this disorder, then the pituitary either becomes overactive or the secretion of the pituitary is not utilized by the ovaries, and hence the typical urinary finding. If the condition were due to pituitary insufficiency, then one would not expect to find an excess of FSH in the urine. In fact, there would be practically none present and even in normals the titer of the substance is so low as to be of little help in routine laboratories where such determinations may be made. There have been one or two exceptions to the finding of an excess follicular stimulating hormone in ovarian agenesis. The author has seen one such case at the age of 18 and has rechecked the urine ten years later, still finding no excess FSH. This finding merely points to the possibility that the absence of FSH

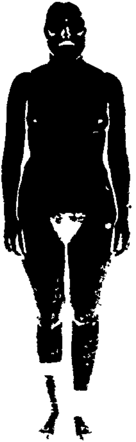


Fig. 11 Cushing's disease, showing purplish striae on hips and inner thighs Note also round face Hirsutism present. Normal catamenia after roentgen therapy



Fig 12 Cushing's disease before and six months after treatment in a young woman with amenorrhea Cured by irradiation of pituitary area A pituitary area dose of at least 4,500 roentgen units should be given in these cases.

is just another congenital anomaly. The adrenal cortices are probably similarly affected, since the total 17-ketosteroid output is often much below normal.

It is important to recognize this syndrome chiefly because nothing can be done about increasing growth rate. The only treatment for ovarian agenesis is administration of estrogens which will cause increased breast growth, and in some instances an increase in pubic hair and menstrual bleeding, providing the uterus is present. Fertility, it seems, is impossible.

Growth hormone is probably not absent in this disorder because of the generally good somatic development, in spite of growth retardation. If growth hormone is present in this syndrome, one can only say that through some congenital abnormality the end organs of the body upon which growth hormones exert their effect are nonreactive.

FEMALE EUNUCHOIDISM

Ovarian agenesis may be contrasted to eunuchoidism. If the ovaries of the normal female are removed because of some disease, or have been rendered inactive by x-ray therapy before puberty, the child continues to grow at a normal rate but does not have the usual spurt in growth associated with puberty and ends up with the usual disproportionate skeletal configuration of the male eunuch; that is, the span is greater than the height and the measurement from the pubis to the floor is greater than from the pubis to the head.

The eunuchoid, on the other hand, is the result of ovarian failure either from disease of the ovary or from selective deficiency of the gonadotropic hormones of the pituitary, just as in males. If eunuchoidism is the result of disease, there will be found in the urine an excess of follicular stimulating hormone very much like the patient with ovarian agenesis. In the eunuchoid woman due to a deficiency of gonadotropin there may be less hair on the body than in the eunuchoid with primary ovarian disease. In this case, as in males, there is an absence or almost complete absence of follicular stimulating hormone. The woman with primary disease of the ovaries causing eunuchoidism may have a normal 17-ketosteroid excretion since these are derived from the adrenal cortex. In the pituitary deficient female eunuchoid there may be less 17-ketosteroid excretion, probably because of a relative lack of some pituitary hormone (ACTH ?) which stimulates the adrenal cortex, hence less sexual hair.

BONE CHANGES

The bone changes in eunuchoidism do not begin to show themselves until around the age of 10 to 14 when the bone age begins to lag in regard to chronological age. By the time the eunuchoid is 18 or 20 years, the epiphyses of the wrists and other long bones have not yet closed, but in spite of the fact that secondary sexual characteristics or menstruation does not occur, these epiphyses eventually close. If such is the case, roentgenograms of the iliac

crest should be made. These epiphyses remain open normally until the age of 20 or 21, but in eunuchoids may be open as late as 40 to 50 years of age.

The x-ray findings in eunuchoidism or in female eunuchs show a general osteoporosis. Compression of one or two vertebrae is not infrequent, which may be quite disabling. If such occurs, there is a further decrease in the height of the trunk, exaggerating the eunuchoid proportions.

Treatment

The only practical therapy in eunuchoidism is the administration of estrogens. This in general is highly satisfactory since it develops breast tissue and usually is considered a worth-while procedure by patients who have been so treated. One would assume that all eunuchoid women have no sexual inclinations, but I have found that this is not always true. In fact in one eunuchoid woman with no sexual development and such marked osteoporosis with compression fractures of the vertebrae, there was apparently a normal libido with orgasm.

Not only should estrogen be given for the psychological effect and for the development of secondary sex characteristics, but also it should be given because it does retard the progression of osteoporosis and facilitates, so it is thought, recalcification. The simultaneous administration of oral methyltestosterone, or other testosterones, may be worth while in patients with osteoporosis and collapsed vertebrae as a measure of increasing anabolism

The eunuchoid, on the other hand, is the result of ovarian failure either from disease of the ovary or from selective deficiency of the gonadotropic hormones of the pituitary, just as in males. If eunuchoidism is the result of disease, there will be found in the urine an excess of follicular stimulating hormone very much like the patient with ovarian agenesis. In the eunuchoid woman due to a deficiency of gonadotropin there may be less hair on the body than in the eunuchoid with primary ovarian disease. In this case, as in males, there is an absence or almost complete absence of follicular stimulating hormone. The woman with primary disease of the ovaries causing eunuchoidism may have a normal 17-ketosteroid excretion since these are derived from the adrenal cortex. In the pituitary deficient female eunuchoid there may be less 17-ketosteroid excretion, probably because of a relative lack of some pituitary hormone (ACTH ?) which stimulates the adrenal cortex, hence less sexual hair.

BONE CHANGES

The bone changes in eunuchoidism do not begin to show themselves until around the age of 10 to 14 when the bone age begins to lag in regard to chronological age. By the time the eunuchoid is 18 or 20 years, the epiphyses of the wrists and other long bones have not yet closed, but in spite of the fact that secondary sexual characteristics or menstruation does not occur, these epiphyses eventually close. If such is the case, roentgenograms of the iliac

Symptoms

The symptoms of the menopause are probably precipitated by estrogen deficiency. When the ovaries fail to respond to pituitary stimulation there then occurs an excess of follicular stimulating hormone in the blood and urine of menopausal females. Whether the vasomotor symptoms of menopause are related to the excess of the follicular stimulating homone or to the absence primarily of estrogenic hormones is not definitely known. In eunuchoid women in their twenties or thirties, at least, with a menopausal type of urine, hot flashes are not commonly seen. In other situations with ovarian deficiency such as ovarian agenesis, or even hypopituitarism, vasomotor symptoms are uncommon. The administration of estrogens to women in the menopause with hot flashes definitely decreases the output of follicular stimulating hormone, although this in itself does not prove that the latter is the cause of symptoms. Other hormonal factors as yet unknown may play a part. The adrenal cortex has been pointed out as being a permissive gland in this situation, but it is still a speculative proposition.

I have frequently observed that many women are treated for various nervous complaints before they have cessation of menstruation simply because they were approaching the age of change of life. I believe that it is probably best to avoid hormonal therapy unless there is present the more reliable symptoms of menopause, and especially hot flashes, excessive sweating with feeling of

and protein tissue, hence bone matrix upon which calcium is deposited. Bone pain may be relieved.

MENOPAUSE

The term menopause obviously denotes the pause of the menses, and as the word is used it implies to most physicians the change of life. Ordinarily the cessation of menses indicates the cessation of ovulation and a lessened estrogen secretion, if not a great reduction in it. However, this is not always the case, as estrogen secretion may continue as shown by a proliferative endometrium and absence of symptoms frequently associated with hypo-estrinism. As every physician knows, some women have cessation of menses at the usual age without noticing hot flashes or difference in their feeling of health or emotional balance.

The menopause may occur at any time after the menarche; in fact it has been suggested that it may occur before the menarche where there has been evidence of secondary sexual development before the onset of the menses. The average age of onset is around 47 to 48 years of age and there are instances of normal menstruation to the age of 60 or even longer.

The cause of the menopause is undoubtedly in most instances the cessation or the exhaustion of available primordial ova which apparently are not renewed throughout life.

Symptoms

The symptoms of the menopause are probably precipitated by estrogen deficiency. When the ovaries fail to respond to pituitary stimulation there then occurs an excess of follicular stimulating hormone in the blood and urine of menopausal females. Whether the vasomotor symptoms of menopause are related to the excess of the follicular stimulating homone or to the absence primarily of estrogenic hormones is not definitely known. In eunuchoid women in their twenties or thirties, at least, with a menopausal type of urine, hot flashes are not commonly seen In other situations with ovarian deficiency such as ovarian agenesis, or even hypopituitarism, vasomotor symptoms are uncommon. The administration of estrogens to women in the menopause with hot flashes definitely decreases the output of follicular stimulating hormone, although this in itself does not prove that the latter is the cause of symptoms. Other hormonal factors as yet unknown may play a part. The adrenal cortex has been pointed out as being a permissive gland in this situation, but it is still a speculative proposition.

I have frequently observed that many women are treated for various nervous complaints before they have cessation of menstruation simply because they were approaching the age of change of life. I believe that it is probably best to avoid hormonal therapy unless there is present the more reliable symptoms of menopause, and especially hot flashes, excessive sweating with feeling of

heat. Occasionally a patient about 40 years of age may develop hot flashes while menstruating regularly and normally and these may be particularly noticeable during the last week or so of the cycle. As the cycle lengthens out to the point of oligomenorrhea, hot flashes may appear and persist for three or four weeks or longer, even several months, but then disappear shortly before or at the onset of a period.

Hot flashes occurring after complete cessation of periods and in situations as described above may be controlled adequately with the administration of estrogen. The oral administration is perfectly satisfactory and the dose of estrogen should be determined by response to treatment. In some instances I have given up to 5 and 10 mg. of stilbestrol a day in order to bring the excessive symptoms under control, following which the dose could be reduced to the usual levels of 0.5 mg. a day.

There are long lists of complaints attributed to menopause, but it cannot always be ascertained whether these are specifically related to estrogen deficiency. It has been estimated that over 80 per cent of women have troublesome symptoms during the change of life. Many of these symptoms are merely aggravated by the onset of change of life. It must be remembered that at this time of life there are a multitude of social, economic, marital and family problems which are conducive to psychic strain and may be equally responsible for many of the symptoms.

In addition to hot flashes and the more prolonged sen-

sations of heat and sweating, the following symptoms may occur: emotional instability, mental depression with its various manifestations, actual psychoses, insomnia, fatigability, and sometimes swelling with chilly-like sensations, anorexia, aprosexia, arthralgia, painful breasts, headache, palpitation, tachycardia, pruritus, frequency, and dysuria.

Some of the changes are undoubtedly related to hormonal deficiencies. There is a tendency for the skin to become drier, less elastic and wrinkled. Head hair and sexual hair may decrease, whereas there may be an increased growth of hair on the face, with a tendency for the breasts to become smaller, with decreased size of the nipple and loss of erectility. There is a tendency for relaxation of the perineal and pelvic muscles with development of urethritis. The vulva may be dry and bothersome pruritus may be present, or even kraurosis vulvae. Trichomonas infections are more common. The membranes of the vagina are less glistening and bleed easily.

OSTEOPOROSIS

Following the menopause and in advancing age, women show a considerable incidence of osteoporosis and this is believed due to estrogen deficiency since the administration of estrogens stops the loss of calcium and may cause some redeposition. The importance of osteoporosis is in the ease of fracture and we see this rather frequently in the spine where there are compressed vertebrae caus-

ing considerable discomfort. The frequency of fracture of the hip in elderly females may in part be a consequence of menopausal osteoporosis.

Treatment

Treatment of osteoporosis consists in administering at least 1 mg. a day of stilbestrol. It is doubtful whether any greater retention of calcium can be obtained by giving more. In addition, testosterone may be administered either buccally or orally or by injection. Three hundred to 500 mg. a month by oral administration should not cause too many masculinization symptoms. I usually recommend 20 to 30 mg. a day taken buccally, or in cases of severe osteoporosis and if considerable pain exists I have given injections of depo-testosterone, 200 mg. weekly for a few weeks, then reduced the dose to 100 mg. twice a month, or the use of buccal tablets in doses of 10 to 20 mg. a day.

At the present time there are several preparations combining methyltestosterone and estrogen in one tablet. Such preparations are perfectly satisfactory and the estrogen and androgen content of these tablets can be determined by the manufacturers' reports. The equivalent of 1 mg. of stilbestrol and 20 to 30 mg. a day of methyltestosterone is the desirable amount to give. There is no particular virtue in the combined tablet other than its convenience.

It is very difficult to come to any definite conclusions regarding results from this form of treatment. It is true that a certain amount of calcium retention has been

demonstrated in the studies of Albright and others giving estrogen and estrogen plus androgen. The recalcification is at best a slow process and will not show by x-ray for a good many years afterward. Because of the age of a good many of these patients it is not easy to follow them and it is the author's impression that few if any such cases have been reported after five to ten years. It is almost impossible to keep all patients on this form of therapy because even without treatment the pain of the above mentioned bony changes subsides spontaneously either through enforced rest or orthopedic appliances such as braces or firm supports. There is no doubt in some instances, as judged by testimony from patients, that the relief of pain is fairly rapid, yet here again one does not know how long the discomfort would have lasted without medication. It is not uncommon to see people with partially collapsed vertebrae without symptoms. There is not much else to prescribe, however, other than support to the back, particularly in elderly patients whose activity, by necessity, is somewhat restricted.

Maximum calcium retention upon estrogen therapy is probably around 150 mg. a day. At this rate it would *require six years or more to replace one fifth of the body* in calcium if the effect could be sustained.

In view of the frequent osteoporotic change in elderly women it would seem desirable that all patients be given estrogens after the change of life. This undoubtedly would prevent osteoporosis if the fundamental hypothesis is correct. The author has met with considerable resistance

ing considerable discomfort. The frequency of fracture of the hip in elderly females may in part be a consequence of menopausal osteoporosis.

Treatment

Treatment of osteoporosis consists in administering at least 1 mg. a day of stilbestrol. It is doubtful whether any greater retention of calcium can be obtained by giving more. In addition, testosterone may be administered either buccally or orally or by injection. Three hundred to 500 mg. a month by oral administration should not cause too many masculinization symptoms. I usually recommend 20 to 30 mg. a day taken buccally, or in cases of severe osteoporosis and if considerable pain exists I have given injections of depo-testosterone, 200 mg. weekly for a few weeks, then reduced the dose to 100 mg. twice a month, or the use of buccal tablets in doses of 10 to 20 mg. a day.

At the present time there are several preparations combining methyltestosterone and estrogen in one tablet. Such preparations are perfectly satisfactory and the estrogen and androgen content of these tablets can be determined by the manufacturers' reports. The equivalent of 1 mg. of stilbestrol and 20 to 30 mg. a day of methyltestosterone is the desirable amount to give. There is no particular virtue in the combined tablet other than its convenience.

It is very difficult to come to any definite conclusions regarding results from this form of treatment. It is true that a certain amount of calcium retention has been

mechanism of this is obscure as well as the mechanism by which testosterone may also accomplish the same temporary result. All that can be said is that the administration of estrogens and androgens in cancer changes the milieu of the body in some way so that either the administration or the withdrawal of these steroid compounds may alter the growth either by speeding it up or retarding it, depending on some unknown effect.

GENERAL TREATMENT OF THE CLIMACTERIC

The treatment of the menopause apart from the treatment of osteoporosis is a general one involving not only hormonal therapy but often sedation. Investigation of the background, social, economic and marital, should be carried out and sound advice and encouragement in the adjustment of such problems should be given. The administration of stilbestrol in doses varying from 0.1 to 0 5 mg. daily is usually satisfactory, although many authors prefer other estrogens and there is no reason for not trying various preparations. Estrone sulfate in doses of 0.3 to 1.2 mg daily, which for all practical purposes is similar to conjugated estrogens, can be used. A very potent estrogen is ethinyl estradiol and the dose of this is 0.02 to 0 04 mg daily

Parenteral therapy is seldom necessary but can be used when oral therapy is not well tolerated or does not appear to be effective, or when the greatest psychological effect of parenteral injections seems advisable. In such cases,

to this proposition from patients as well as physicians. One of the objections, of course, is the fear of hastening or producing cancer of the breasts or possibly cancer of the female generative organs by continued use of estrogens. This fear I do not believe is entirely justified. Considering the number of women who have been taking estrogens during the past ten or fifteen years, one would expect a great increase in the incidence of cancer of these organs.

ESTROGEN AND CANCER

The late Dr. Nathanson who had an extensive experience in the administration of estrogens and androgens for metastatic carcinoma of the breast as well as for localized cancer of the breast without metastases felt that there was no greater incidence of cancer in the other breast as a result of taking estrogens than in the normal population. It was his opinion, often expressed personally to the author, that if there is such a thing as a precancerous lesion (possibly "cancer in situ") or if the patient is destined to develop cancer of the breast, estrogens might very well speed up the growth into an active cancer. On the other hand, large doses of estrogens may have a suppressive action on the development of cancer of the breast and its metastases, the mechanism of which is obscure. Clinical experience has shown that in cancer of the breast with metastases, ovariectomy and even adrenalectomy has temporarily retarded the cancerous growth. The

tives such as barbiturates or barbiturates and estrogens and in some instances placebo therapy has seemed to be effective, but in the author's experience, in trying out the synthetic preparations some years ago, it was impossible to use placebos for any length of time without a return of symptoms.

After a satisfactory dose of estrogens has been given, particularly to control hot flashes, it may be necessary to reduce this dose because of vaginal bleeding. This often presents a problem, and I am not of the opinion of many surgeons who feel that every woman past the menopause who is taking estrogens should be rushed to the hospital for a dilatation and curettage. It is more sensible to discontinue the estrogens for a period of a month or so and if no further bleeding occurs, then the amount can be readministered in approximately half dosage. This advice is given only if there is no evidence of abnormality on pelvic examination and if the Papanicolaou smear of cervical secretions is negative for cancer cells.

There are a few side effects of estrogen therapy such as nausea, or anorexia in certain individuals but by and large this is not a common occurrence in treating menopausal women. Some women develop some breast discomfort, occasionally skin eruptions, purpuric-like, but as a rule these disappear quickly upon omission of the preparation. One estrogen or another may be tried, or one can revert to the use of smaller doses of estrogen combined with androgen.

The menopausal symptoms may last for fifteen to

10,000 to 20,000 rat units of estrogen can be given once every week to two weeks if necessary. Pellets of estrogens have been tried out and are effective but are hardly necessary.

For vaginal complaints such as irritation and discharge or easy bleeding, vaginal suppositories may be used, each one usually containing about 2,000 I.U. These are used nightly.

In regard to the duration of therapy there is considerable difference of opinion. Some believe in continuous therapy, and the author is of this opinion, while others give estrogens until hot flashes have subsided and then therapy is omitted until they return. There is no real objection to this form of therapy if it is effective.

The administration of methyltestosterone either orally or buccally, or the administration of testosterone intramuscularly, is effective in controlling menopausal symptoms if estrogens are not tolerated.

As said before, at the present time there is considerable literature on the use of combined tablets containing both estrogen and androgen. It is believed that they have a greater anabolic effect as well as minimizing the complications of estrogens.

Irradiation of the pituitary in patients with menopause has been tried on the basis that the pituitary is oversecreting follicular stimulating hormone. Favorable results have been claimed, but it is not to be recommended as a routine treatment.

A good many women can be relieved by simple seda-

TESTES

CRYPTORCHIDISM

Cryptorchidism may be defined as a hidden or an imperfectly descended testis, that is, the failure of one or both testes to descend into the scrotum. It is to be distinguished from pseudocryptorchidism, testicular agenesis, or anorchism, and occasionally pseudohermaphroditism and ectopic testes. Cryptorchidism occurs apparently in one of 30 boys or in 218 of 10,000 autopsies. It was found in approximately one of 250 adult men, being bilateral in only 10 per cent. The testes are in the scrotum in two thirds of newborn children and in 90 per cent of children at four months. There are often other congenital anomalies in cryptorchidism, particularly in anorchia of which one finds about 26 cases in 10,000 autopsies. The cause of cryptorchidism may be a congenital defect or mechanical abnormalities of various parts of the genital apparatus. The testis may not descend into the canal for this reason. Usually a tight ring is to be found. Some believe that cryptorchidism is due to short spermatic cords or gubernacula, but others do not believe this has any particular effect on failure of testes to descend. The exact cause of descent is not known. Some believe it may be the down pull of the cremasteric muscle. It is thought that inadequate development of the scrotum and of the inguinal canal are essential prerequisites.

twenty or more years after the onset of the menopause or may be very mild and disappear within a few years. It has often been noted that upon discontinuing estrogens in women who have had rather severe symptoms, the rebound is quite marked. The only alternative here is to resume the use of estrogens, omitting them from time to time to see if there is need for their continuation unless one feels that they should be administered for a long period as mentioned above. In some instances with extreme hot flashes and excessive sweating where ordinary doses of estrogens do not appear to be effective, it is legitimate to increase the dose even up to the administration of 5 mg. of stilbestrol or its equivalent in other estrogens daily until control is obtained. After this it is probable that the dose can be gradually reduced.

There are several preparations available which are said to have an excellent effect on the symptoms of menopause with less chance of menstrual bleeding. If these preparations are carefully assayed, it will probably be found that the estrogen is weaker milligram for milligram than the standard preparation. As an illustration, ethinyl estradiol is fifty times stronger than estrone and ten times stronger than diethylstilbestrol. Estradiol which probably represents the true hormone of the ovary is twice as strong per milligram of weight as diethylstilbestrol.

until the secretion of pituitary gonadotropic hormones develops, which is usually around twelve to thirteen years of age but may occur before, so that generally the test is of little value before one would expect these hormones to be elaborated.

Complications that arise from crytorchidism consist of inguinal hernia, torsion, tubular atrophy and aspermatogenesis. It is thought that in 11 to 15 per cent cancer develops in the undescended testis later in life, but opinions differ. Also there is greater danger of trauma to testes located in the inguinal canal.

Treatment varies. It might be said that the treatment depends primarily on the development of Leydig cells which can be stimulated by chorionic gonadotropin. Since in two thirds of patients with cryptorchidism the testes will develop spontaneously later in life, the decision is often difficult to make. There is, however, no harm in a trial course of chronic gonadotropin at five or six years of age. If the testes fail to descend with chorionic gonadotropin therapy, testosterone orally also may be tried. If there is no descent then it can be concluded that the cause of the cryptorchidism, barring any gross endocrine disturbances, is mechanical blockage, short spermatic cords or testicular agenesis.

The dosage of chorionic gonadotropin varies considerably, probably 300 units each week is sufficient for young children; up to 2,000 or 3,000 units may be worth trying in adolescents. The use of oral testosterone for a period of eight to twelve weeks may be effective when chorionic

When no anatomical abnormalities are present there seems to be little doubt that there is some hormonal influence in their descent. In those patients who respond to hormonal treatment, it would appear obvious that the hormonal influence is predominant. Perhaps androgenic hormones during pregnancy may have caused descent into the pelvis and the scrotum. It is well known that the testis does have interstitial cells at birth which disappear shortly afterward and therefore, the testes themselves may secrete active hormone into the fetal blood stream; when this hormone is lacking the testis may not descend. Its continued failure to descend after birth may be due to endocrine disturbances occurring then. Such disorders as pituitary dwarfism, cretinism, diabetic dwarfism, Laurence-Moon-Biedl syndrome and others may lack the necessary stimulus for descent later.

True cryptorchidism should be distinguished from pseudocryptorchidism which is recognized by the fact that the testes may be in the scrotum at some time and not seen at other times. Exposure to cold and nervousness may cause them to go into the canal. Diagnosis is made by history, previous examination, relaxation by submerging in a warm bath or application of suction to the gubernaculum in the scrotum.

The diagnosis of testicular agenesis can be verified only by surgical exploration. Usually other signs appear at the usual age of pubescence or adolescence, when eunuchoid skeletal signs become manifest In testicular agenesis, an excess of FSH may be found but this may not be present

Table 1
CRYPTORCHIDISM IN BOYS
10,712 Autopsies (Campbell)

Intra-abdominal	61
Inguinal ring	20
Canal	156
Pelvic brim	2
Retroperitoneal	1
External ring	10
Not found	30

Table 2
CRYPTORCHIDISM IN BOYS
10,712 Autopsies (Campbell)

Other urogenital anomalies	92
Other nonurogenital anomalies	175
Congenital hernia	Over 50%

Table 3
LOCATIONS OF ECTOPIC TESTES

1. Interstitial
2. Femoral
3. Base of penis above pubis
4. Perineal
5. Transverse
   (both on same side)

and thus the Leydig cells will fail to develop In these cases, however, it is possible that the failure to develop might be a congenital defect.

Another argument for surgery is that oftentimes the

gonadotropin fails or it may primarily cause descent of the testes. In some instances both may be tried together.

Surgical indications are as noted above, that is, when hormone therapy has failed or hernia is present. The age at which operation is performed varies greatly but it should probably be done about the twelfth or thirteenth year. The Torek procedure is the accepted method but is not universally successful when short cords are present, and in an attempt to bring the testes into the scrotum the blood supply may be interrupted, followed by atrophy of the testes

Some physicians do not believe there is necessity for treatment before the age of fourteen or fifteen. It is believed that those testes which do respond to chorionic gonadotropin will descend anyway. However, early therapy allows the testes to come down through the canal before it is too large. In many instances, the testes do not increase much before pubescence which may conservatively be estimated at around ten to twelve years of age.

It is stated that congenital hernia is present in over 50 per cent of the cases and this in itself is reason for operation.

There are social or mental reasons for instituting therapy because of the consciousness of the deformity in boys who play together.

Another argument for early operation is the fact that because of the associated abnormalities, especially in bilateral cryptorchidism, there is interference with circulation which may decrease the blood supply to the testes

Table 1

CRYPTORCHIDISM IN BOYS

10,712 Autopsies (Campbell)

Intra-abdominal	61
Inguinal ring	20
Canal	156
Pelvic brim	2
Retroperitoneal	1
External ring	10
Not found	30

Table 2

CRYPTORCHIDISM IN BOYS

10,712 Autopsies (Campbell)

Other urogenital anomalies	92
Other nonurogenital anomalies	175
Congenital hernia	Over 50%

Table 3

LOCATIONS OF ECTOPIC TESTES

1. Interstitial
2. Femoral
3. Base of penis above pubis
4. Perineal
5. Transverse
   (both on same side)

and thus the Leydig cells will fail to develop. In these cases, however, it is possible that the failure to develop might be a congenital defect.

Another argument for surgery is that oftentimes the

cryptorchid testis is silent and imbedded in adhesions, thus preventing the testis to descend if amenable to chorionic gonadotropin.

As often happens after treatment, the testes may re-ascend in the canal. In such a case one does not need to be alarmed since the testes will probably respond to the normal pubescent stimulation and descend. The fact that they come down with chorionic gonadotropin is a good indication that they will descend spontaneously later.

MALE EUNUCHOIDISM AND EUNUCHISM

The term eunuchoidism as generally used now is applied to males as well as females who have gonads but in whom there is little or no function of the Leydig cells in the male testes and absence of estrogen secretion by the ovaries of the female. A male eunuch is defined as a man or a boy who has been deprived of the testes or external genital organs.

Skeletal Alterations

The physical alterations of the eunuch and eunuchoid are very similar and have been observed for many years. It was the custom in earlier times to castrate boys in order to maintain their soprano voice, it was also practiced on guardians of harems or for religious beliefs. The physical alterations in the skeleton depend on the degree of development at the time of castration. If the boy is castrated before puberty he is likely to show general dispro-

portion of his skeleton in that the epiphyses do not close, the extremities grow much longer in proportion to the trunk and the span as measured between the tips of the fingers of the outstretched arms is often from 1 to 6 inches greater than the height. The distance from the floor to the base of the penis or pubic bone is greater than the distance from the pubis to the top of the head, which in normal individuals is approximately the same.

Generally speaking, there is no cessation of growth or any puberal spurt in growth in the eunuchoids. In the absence of the puberal spurt, a boy at the age of 14 or 15 may actually be shorter on the average than normal boys of the same age. They continue to grow for a longer time and may reach heights of 6 feet, sometimes 6 feet, 6 inches, depending in some instances on the family tendency for tallness. Eventually there is a cessation of growth, even though the epiphysial lines may still be present at the age of 35 or 40. The last epiphyses to close, namely the iliac crests, may still be unfused at 50 or 60 years of age.

On examination, the prepuberal castrate or the eunuchoid young adult retains his preadolescent look, in which there are very little beard, softness of the skin, absent or scanty pubic and axillary hair, and a high pitched voice.

The bodily contour of eunuchoids may be feminine as it frequently is in boys before or during puberty. There is an abundance of fat on the mons, some hippy obesity and sometimes swelling of the breasts. On the other hand, the eunuchoid may not display these abnormalities, just

as some normal boys before puberty have an entirely masculine contour. I do not believe that the contour indicates whether there is a primary disease of the testes or a selective deficiency of pituitary gonadotropins which maintain Leydig cells and tubules of the testis.

The patient with eunuchoidism or even eunuchism is not inclined to consult a physician because of lack of sex interest. Since the latter is not present, he does not particularly feel the need of it. Often he consults a physician for some other reason and many persons may not know anything about this condition until late in life. Surprising as it may seem, they occasionally get married and then consult a physician because of the predicament that they are in, especially on urging from the wife.

The eunuchoid is apt to be sensitive, shy and often displays many neurotic tendencies based either on the lack of the male hormone directly or upon the consciousness of his dissimilarity to other boys or men of his age.

The young eunuchoid male will have testes smaller than average, but if they are firm and not greatly decreased in size there may always be a possibility of spontaneous puberty later in life. If the testes are miniscule or only a gubernaculum is felt, the boy either has undescended testes with failure of Leydig cells or they may be the seat of a disease in which the Leydig cells as well as the tubular function have been completely suppressed.

Young males with undescended testes generally have secondary sexual development because the Leydig cells

do not degenerate as compared to the tubules. Eunuchoidism can be associated with cryptorchidism, but the two are not necessarily related. Some eunuchoids may have anorchia, but this is determined only by operation

The problem in differentiating a boy with late pubescence and an early eunuchoid is a difficult one. Since it is well known that boys may not have puberty even to the age of 18 or 19, following which time they may go through adolescence, there is always some doubt about treating a boy of 15, 16 or even 17 with hormones In the study of these boys, an x-ray of the wrist for bone age or, if the eunuchoid is over 20 years of age, x-ray films of the ilium or iliac crests should show retardation of the epiphysial closure Comparison should be made with available standards, and retardation of at least two years is probably of significance, but not too much importance should be placed upon a bone age retardation under two years because of the great variation in normal boys up to adolescence Up to around 10 to 14 years, the bone age may correspond to the chronological age, but after this time a significant lag in bone age takes place in pure eunuchoidism

Tests of Gonad Function

The injection of chorionic gonadotropin, 500 to 1,000 units three times a week for a period of two to four weeks, will as a rule cause increased size of the testes and erections, with some growth of the penis. If such develop-

ment does not take place, it can be assumed that the fault lies in primary disease of the testes and not from a selective deficiency of pituitary gonadotropins. If urine can be assayed for 17-ketosteroid excretion, the administration of chorionic gonadotropins should double the twenty-four output if the disease is not primarily in the testes. But if disease is in the testes, there should be no increase in the 17-ketosteroid excretion.

Another laboratory method for the differentiation of these two types of eunuchoidism is in the assay of the urine for follicular stimulating hormone. If the hormone is present in excess, the chances are that the trouble is primarily in the testes, but if the titer of follicular stimulating hormone is low or none can be demonstrated, it can then be assumed that the trouble is primarily in the pituitary. From a practical point of view, it actually makes little difference as far as therapy is concerned.

Differential Diagnosis

To be differentiated from eunuchoidism is hypopituitarism. There is usually little difficulty in this because of the proportionate nature of the skeleton in the hypopituitary case, the usual dwarfism, the much greater retardation of bone age and the lowered inorganic serum phosphorus if the patient is below the age of 10 or 12. If hypopituitarism has existed for a long time, the marked dwarfism is sufficient to distinguish the case from eunuchoidism. If it is in the person who has perhaps reached a fairly normal stature before the onset of hypopituitarism and if

the duration of the disorder has not been more than a few years, there should be some difficulty. By hypopituitarism is meant deficient pituitary secretion in addition to gonadotropic deficiency.

Klinefelter's Syndrome

The manifestations of eunuchoidism are the result of *testicular deficiency of testosterone. The testes are made* up of two components, the Leydig cells and the tubules. Gonadal deficiency, therefore, may be of two types. There may be only destruction of the tubules with normal Leydig cell function. This may result in a condition known as *Klinefelter's syndrome characterized by* aspermia and gynecomastia. There are other cases of aspermia in perfectly normal males without gynecomastia. In addition, there is still another congenital condition with aspermia in which by testicular biopsy there is an absence of the germinal cells which are required for spermatogenesis, but with Sertoli cells present. These cases may have some deficiency of Leydig cell secretion, but are not affected with gynecomastia. As it can be seen, there are gradations from ordinary eunuchoidism to Klinefelter's syndrome, but the very description of the pure type of case, as in all disease, helps in the differential diagnosis.

The testes in Klinefelter's syndrome are soft, atrophic and smaller than normal. The patient usually has normal secondary sexual characteristics, that is, normal sized penis, normal potentia and libido. Breasts are consider-

ably enlarged. These cases, whenever discovered, are not usually diagnosed until after the age of 16 or more because of the frequent occurrence of enlargement of the breasts during the preadolescent period. Great excesses of follicular stimulating hormone are found in the urine in Klinefelter's syndrome and the 17-ketosteroid output is normal or perhaps slightly below normal. Testicular biopsy shows aggregates of Leydig cells, sometimes appearing almost as small adenomas, while there is hyalinization and scarring of the tubules In some cases of Klinefelter's syndrome, Leydig cell function may gradually be reduced or lost, at which time they can be treated with testosterone, but there is no treatment for aspermia in this disorder. The only treatment for gynecomastia is plastic repair which is justifiable if the patient's embarrassment is sufficient

"Fertile Eunuchs"

McCullagh has recently described a group of males whom he terms fertile eunuchs. These men show spermatogenesis in adequate quantities, yet have some of the skeletal proportions of eunuchs and decrease in secondary sexual characteristics, including reduced libido. This is surprising in view of the fact that it has always been believed that the tubules require not only follicular stimulating hormone for their maintenance and maturation of spermatozoa, but also testosterone. Treatment of symptoms of Leydig cell deficiency, of course, is administration of testosterone.

Treatment

Testosterone is the treatment of choice in eunuchoidism, but if there is response to chorionic gonadotropin it could be continued in doses of 3,000 units a week over a period of a year with the administration of buccal testosterone in doses of 10 to 20 mg. per day. The author has observed 3 men who have remained stationary as regards sexual development, 2 of whom showed skeletal proportions of a eunuchoid while one definitely had hypopituitarism, who responded to testosterone or a combination of testosterone and chorionic gonadotropin with further development of the testes, spermatogenesis and proven fertility. These cases, however, are the exceptions to the rule that fertility is unlikely.

Testosterone may be administered either orally or buccally in eunuchoidism or eunuchs. Buccal tablets are placed under the tongue or under the upper lip or in the cheek beside the teeth They dissolve slowly and do not interfere with eating, drinking or talking. Testosterone may be injected once or twice a week in the form of propionate, but with the advent of testosterone cyclopentylpropionate, known as long-acting or depo-testosterone, an injection twice a month may be perfectly satisfactory. If the propionate is used, 20 to 50 mg. a week is adequate and if the long-acting testosterone is used, 100 to 200 mg. every two to three weeks is ample.

I have also used testosterone pellets in many cases and these are preferred by some patients because they do

not have to bother with injections or daily dosage of testosterone. These can be implanted under the skin on the anterior aspect of the thigh or in the back behind the shoulder blade. I prefer the anterior thigh because of its accessibility at all times. Four pellets of 75 mg. each is a satisfactory amount to implant in eunuchoids after the age of 18 or 20. Six pellets may be given without annoying priapism. The pellets last from two to three months and the patient can usually tell when the pellets are becoming exhausted by the decreased number of erections, by some loss of weight, and in some patients an increase in fatigability and decreased endurance. If the pellets seem to lose their effect within a month or so, it is probable that they have been surrounded by a fibrous capsule, but this rarely happens. Once or twice in my experience one or two pellets have become extruded.

Technique of Pellet Implantation

There are various methods of implanting pellets, all of which are office procedures. The author's preferred method is to use a trocar of large enough bore to allow a pellet to pass through it. A small incision about 1/4 inch long is made in the thigh after infiltration with novocain, and with a long needle, novocain is injected through the incision under the skin for a distance of about 1½ inches. When the novocain has taken effect, the trocar is inserted to a depth of about two inches, the plunger or stilette withdrawn, and the pellet, after being dipped in sterile saline solution and rolled in sulfa powder, is placed in the

trocar and pushed in with the stilette to its location. Another pellet may be inserted in the same avenue after withdrawing the trocar about 1/4 inch. It has been my custom to implant only two pellets in each avenue; if four pellets are to be used the trocar is pushed in the opposite direction through the incision. If six pellets or eight pellets are used, then the trocar is inserted laterally at right angles to the previous implantation through the incision. After implantation, the wound edges are pulled together by stretching the skin from either end of the small incision, a small piece of adhesive with a very small hole is placed over the incision, thus holding the edges together. The small hole in the adhesive is allowed for the escape of the serum should such occur. Over the adhesive is placed a fairly good sized sterile pad which is also strapped down with more adhesive strips. Occasionally, with unexpected exertion after leaving the office, the adhesive covering the wound may come off and bleeding may take place. Because of this possibility, the patient remains lying down for twenty minutes or so, especially if there has been a tendency to bleed during the implantation.

The response to testosterone as regards libido and potentia varies considerably and in some instances in castrated males or even in eunuchoids there has been no appreciable benefit in this regard. Usually, however, there is an increase in the size of the penis, but this is less likely to occur in older individuals than in younger ones. It would seem that the end organs lose their capacity for

growth with increasing age. Growth hormone, I do not believe, renders a permissive action because testosterone alone may cause considerable development of the external genitalia in definite cases of hypogonadism.

Patients with eunuchoidism should not be too hopeful regarding a sudden change in sexual development. It should be pointed out that the period from pubescence to adolescence requires four or five years and that it should take this long for the state approaching maturity to develop. Initially, however, there is almost at once an increase in erections and in a month or two an increase in self-confidence and endurance. The appearance of a beard in eunuchoids is probably delayed longer than would occur in normal males through the adolescent period. In fact, I have rarely seen a eunuchoid who has developed satisfactorily in other ways have a beard anywhere near that of the average man.

The problem of sterility may arise because some eunuchoid men may marry and the majority of them will be sterile This should be pointed out to them if during treatment there is no tendency for the testes to increase in size. Testicular biopsies or sperm counts can be carried out as in any other case of sterility. As the eunuchoid grows older he develops more of the characteristics of long-standing eunuchs, namely, wrinkling of the skin, often called crow's feet, wrinkles of the face, sometimes premature graying of the hair and osteoporosis to the extent there may be fractures or compression of vertebrae. In a few elderly eunuchoids, that is, past 50 years of age,

whom I have treated, the usual doses of testosterone have caused too much priapism so that the oral administration of not more than 10 mg. of methyltestosterone a day was necessary to avoid this. They admit to a better sense of well-being and more endurance even on this amount of testosterone.

STERILITY

By definition, sterility means inability to reproduce, whereas the term infertility, which may be a better one in many instances, denotes any reduction in fertility. Basic infertility, or so-called primary barrenness, is said to be present after two or more years of marital life with normal intercourse and without contraceptives The term secondary sterility signifies that conceptions fail to result in a viable offspring, or following a previous normal pregnancy, there have been three or more years of involuntary barrenness.

Absolute sterility indicates that conception is impossible because of major congenital or acquired defects, whereas relative sterility or infertility infers conception is probable when certain recognized factors are corrected.

Certain couples may have a higher fertility index than others as shown by remarriage in which, although no abnormalities had been discovered, both readily are able to bring about conception with a second partner.

Generally speaking, patients who seek advice because of inability to have children do not constitute a group of

gross endocrine disturbances. When such is present, the disorder may be suggested by abnormally short stature, secondary sexual retardation, primary amenorrhea or late menarche followed by scanty or irregular periods with or without hirsutism, and organic loss of sexual desire or impotency. In contrast to the rare organic variety, a loss of libido or potentia is not an uncommon complaint in the infertile male with psychoneurosis and in some instances this may be the sole cause of barrenness since it represents an inability to perform the marital act.

PLAN OF STUDY

As a rule it is the female partner who seeks advice and when a thorough history and physical examination show no medical disease or obvious gynecologic cause or absolute sterility, the first step is to request that the male partner accompany the patient at the time of the next designated appointment for a general physical examination, at which time a semen specimen should be brought in for evaluation. When impossible, the alternative is to request that the husband submit a semen specimen for study at the time that the necessary instructions, procedures and appointment dates are discussed with the patient.

To complete the essential diagnostic procedures and yet condense the period of study, especially for couples living at a distance, the female partner, even though her periods are normal, should return for an endometrial bi-

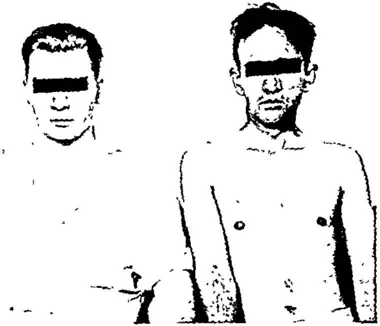


Fig 13 Addison's disease (right) showing pigmentation, especially of fore-neck and arms, although a diffuse tanning of the entire body. Ink black freckles present as well as pigmented areas in mucous membrane behind lips

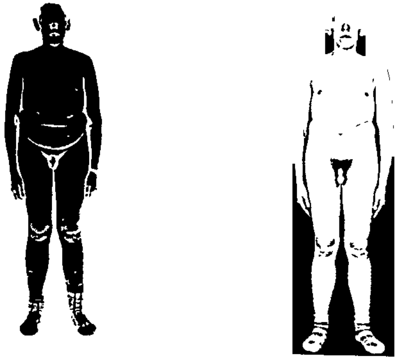


Fig. 15 Eunuchoidism in a male, 24 years old. Treated with testosterone cyclopentylpropionate, 200 mg. intramuscularly at three weeks intervals No enlargement of testes took place. Married but sterile.

opsy within three days of her expected period to determine if ovulation occurs as shown by a progestational endometrium. This procedure, plus evaluation of the sperm specimen, can readily be accomplished at this second office visit. Since ovulation normally occurs about fourteen days before the onset of the next menstrual period, regardless of the length of the cycle, the number of days between the date of the biopsy and the first day of the subsequent period must be known to interpret properly the endometrial findings, especially when the menses are somewhat irregular. As an example, if an endometrial biopsy taken on the twenty-sixth day of a twenty-eight day cycle should show a partially secretory response consistent with the seventh postovulatory day, there may have been an inadequate endometrial response to normal progesterone levels or a premature regression of the corpus luteum and/or insufficient progesterone secretion. However, if the period were a week late, this mid-secretory pattern would indicate normal ovarian function since the biopsy would have been obtained about seven days before a complete progestational response of the endometrium could be expeced.

BASAL TEMPERATURE CHARTS

Normal basal temperature charts, when taken accurately, will not only signify the presence of ovulation but will also show the most opportune time for conception to take place. Basal temperature charts are not a substitute for

the endometrial biopsy unless the latter cannot be performed, because the endometrial biopsy is a more reliable index of ovarian function and in addition, this procedure determines the responsiveness of the endometrium to the ovarian hormones elaborated. Although the most convenient and informative method available for dating the time of ovulation, temperature graphs are often of limited value since many charts show such a grossly irregular pattern as to defy interpretation until the thermal shift is nearly complete and the probable time for conception has passed.

Oral temperatures must be taken before arising in the morning with the thermometer kept in place for at least three minutes and the temperature recorded on a graph used for this purpose. Since successive temperature charts show similar characteristics when normal but are rarely if ever identical in all respects, basal temperatures must be taken for a minimum of two or three months, during which time any minor infection or symptoms during the menstrual cycle, as well as the time of intercourse, must be appropriately recorded for proper interpretation. Typically, basal temperatures remain at relatively low levels until approximately fourteen days (plus or minus two days) prior to the first day of the next period, at which time the temperature will be as low or slightly lower than on any previous date. A variable rise in temperature from 0.4 to 1 degree then occurs over a period of three to six days. Although some think that the temperature shift bears no consistent relationship to ovula-

tion as judged by single artificial insemination experiments, and claim that ovulation may occur two to three days before or after the temperature change, most agree that ovulation usually occurs within five to thirty hours of the initial temperature rise as judged by scheduled laparotomy or direct culdoscopic observation. Following the temperature shift, these higher temperatures are maintained until approximately two days before the period, at which time the temperature starts to decline providing pregnancy has not taken place.

CERVICAL SECRETIONS

Cyclic variations occur in the cervical secretions which are quite marked and the characteristic pattern noted near the time of ovulation can be correlated with the thermal rise as noted on the patient's temperature graph for that particular month. At the approximate time of ovulation, the cervical mucus is thin, clear, abundant and when allowed to dry on a glass slide, a fern-like crystallization will be observed. At this stage, the cervical mucus is more receptive to the sperm than at other times during the menstrual cycle and when a drop of cervical mucus is placed in contact with a drop of semen and covered with a cover slip (Kurzrok-Miller test), the sperm cells will generally show good motility in a forward and branching directional pattern through the cervical mucus as contrasted to a more purposeless course observed in the semen sample.

There are more elaborate methods for studying the ovulatory and postovulatory menstrual phase such as the rat test of Ferris which estimates the amount of urinary pituitary gonadotropins just a few days preceding ovulation, the determination of pregnanediol by assays, and repeated vaginal smears for luteal changes, but these are not practical in general practice.

COLLECTION OF SEMEN

As was mentioned, the female partner following her physical examination should be instructed as to the method of collecting the semen specimen since in all probability, she will bring this specimen to the office at the time that the endometrial biopsy is performed. A clean test tube with a cork stopper should be provided, with printed instructions. The specimen should be collected, after four or five days of abstinence, in a clean and dry widemouthed container after coitus interruptus. The sample is then transferred to the sterile test tube with a cork stopper and the patient is instructed to bring this to the office within an hour after its collection. It should be carried close to the body to keep the temperature as near the normal body temperature as possible.

For religious reasons, some patients are not permitted to collect specimens in this way, in which case the curved plastic spoon of Doyle can be used. This device is inserted just prior to intercourse, the distal portion of the spoon resting in the posterior fornix just beneath the cervix.

The coital specimen is retained in this spoon in adequate amounts for proper evaluation. Immediately after intercourse, the spoon is withdrawn and the contents emptied into the sterile tube. Although the semen is mixed with some cervical and vaginal secretions and usually does not represent the entire semen volume, these variations in the semen analysis are of little practical importance.

EXAMINATION OF SEMEN

In examining the specimen, the viscosity is estimated by the tenacity of the specimen when an applicator or loop is withdrawn from the surface of the fluid. In determining the number of sperm cells per cubic centimeter, the usual white blood cell pipette is used and the semen is drawn up to the 0.5 mm. mark and diluted with 1 to 20 saturated solutions of sodium bicarbonate and 1 per cent phenol. A representative drop is placed on the ordinary blood counting chamber and the spermatozoa are counted in five blocks of sixteen squares each, to which number six ciphers are added.

The average semen volume is approximately 4 cc. If the specimen has been collected as an office procedure, it should be allowed to stand for fifteen to twenty minutes at room temperature, during which time liquefaction occurs and the viscosity of the specimen is decreased. The average count in the fertile male is usually from 80,000,-000 to over 100,000,000 sperm cells per cubic centimeter, but in view of studies showing the group with over 100,-

000,000 sperm per cubic centimeter to be only 2 to 3 per cent more fertile than the group with 60,000,000 to 100,-000,000 sperm cells, and in view of the appreciable drop in the percentage of conceptions as the number of sperm cells decreases below this figure, it is generally agreed that 60,000,000 sperm cells per cubic centimeter is the lower limit of the normal sperm concentration.

From 80 to 90 per cent of normal sperm are motile for two to four hours at room temperature. After twenty-four hours approximately 10 per cent of these sperm cells should exhibit at least sluggish motility. Attempts to evaluate the type or the directional activity of the sperm cells in the semen sample are no criteria of normalcy, providing the initial motility is highly active, since a suspiciously abnormal motility pattern may show no deviation from the normal when these sperm cells are deposited in a drop of normal cervical mucus.

In addition to decreased numbers, the percentage of abnormal sperm is of marked importance in the evaluation of male fertility and the combination of these two factors constitutes the basic criteria in the evaluation of the degree of infertility present. A semen specimen with 20 per cent abnormal forms must be considered normal providing the sample contains 60,000,000 sperm of normal morphology and aggressive motility. Thirty to 40 per cent abnormal morphology represents an appreciable decrease in fertility and the degree of infertility rises in direct proportion to progressive increments in abnormal cellular forms. The most frequently observed morpho-

logic aberrations consist of those sperms with definitely tapered heads, those with crook or wry necks, giant or pinhead forms and those with cellular appendages involving the neck or junction between the head and tail.

An accurate appraisal of the degree of infertility as judged by the semen analysis from a male partner with no physical disease is obviously impossible at present since both the underlying cause and the altered basic biologic phenomena remain unknown in the vast majority despite the investigative studies performed. As a result, the evaluation of the semen analysis is fundamentally based on the conclusions gained from the study of large series of infertile and sterile semens. In this respect, it has been shown that further reductions in the fertility index as evidenced by significant falls in conception potential occur with each additional increment in semen deterioration which is characteristically evident by an increased incidence of abnormal forms accompanied by a decrease in total sperm population and a drop in the percentage of motile cells. Although individual variations in sperm population are frequent, this general ratio of abnormal cell structure to decreased total cells and motility may be roughly traced downward from the completely normal semen analysis to complete azoospermia.

Although the criteria derived from extensive observations are of distinct value, these generalizations when appraising the semen analysis of a relatively infertile male partner are of relatively little prognostic significance. Due to such intangibles as a subsequent variation

in the sperm count for no apparent reason, or perhaps an improvement in the female cervical secretions to permit conception with the husband's status unchanged, there are too many unknowns to permit the statement other than an indefinite approximation providing the degree of relative infertility is not too pronounced.

In the presence of an illness or after some acute toxic process, a semen analysis may not give a true picture for a period of perhaps two months. Since it would appear that sperm mature in approximately three weeks after development, a toxic influence which might affect the sperm count may not be evident for at least ten days, at which time some depression of spermatogenesis may be noted. This effect would probably be maximal in about four weeks and the semen analysis return to normal after a period of about six to eight weeks.

BLOCKAGE OF VAS DEFERENS

Should the male have normal sexual drive and potency with testes of normal size and consistency but with a semen specimen showing no evidence of spermatogenesis, it is necessary to exclude the possibility of blockage of the vas deferens. If the testicular biopsy shows normal spermatogenesis and numerous sperms in the epididymis, injection of the vas at the time of the testicular biopsy with methylene blue or a similar substance will demonstrate the presence of this blockage if this dye fails to appear in the urine. In the presence of blockage of the vas

a plastic operation consisting of a vaso-epididymal anastomosis may be feasible, in which case there is about a 30 per cent chance of fertility in successful cases.

In tubular disease of the testes with normal Leydig cell function in which potency and libido are normal, the testes are smaller and somewhat softer than normal. A testicular biopsy will demonstrate the situation which may or may not be associated with aspermia or at least oligospermia. In some instances the examination of the testes will be perfectly normal. When there is spermatogenesis but with incomplete maturation of the sperms or what is known as "an arrest" at one or two stages of development, a testicular biopsy may afford some means of deciding what type of therapy, if any, should be employed.

VAGINAL AND CERVICAL FACTORS

Should fertility be demonstrated in the male, then the female partner should be further investigated. It is to be assumed that there may be dyspareunia or vaginismus, in which instance adequate penetration is not possible. Local conditions of the cervix may interfere with conception and should be taken care of. In addition to trichomonal or fungus infections of the vagina, there may be endocervicitis, cervical erosions, polyps, or cervical stenosis. Although any cervical or vaginal infection should be treated when present, it should be noted that sperm, when deposited in the vagina, are placed in a physiologically hostile environment under normal circum-

in the sperm count for no apparent reason, or perhaps an improvement in the female cervical secretions to permit conception with the husband's status unchanged, there are too many unknowns to permit the statement other than an indefinite approximation providing the degree of relative infertility is not too pronounced.

In the presence of an illness or after some acute toxic process, a semen analysis may not give a true picture for a period of perhaps two months. Since it would appear that sperm mature in approximately three weeks after development, a toxic influence which might affect the sperm count may not be evident for at least ten days, at which time some depression of spermatogenesis may be noted. This effect would probably be maximal in about four weeks and the semen analysis return to normal after a period of about six to eight weeks.

BLOCKAGE OF VAS DEFERENS

Should the male have normal sexual drive and potency with *testes of normal size and consistency* but with a semen specimen showing no evidence of spermatogenesis, it is necessary to exclude the possibility of blockage of the vas deferens. If the testicular biopsy shows normal spermatogenesis and numerous sperms in the epididymis, injection of the vas at the time of the testicular biopsy with methylene blue or a similar substance will demonstrate the presence of this blockage if this dye fails to appear in the urine. In the presence of blockage of the vas

from pelvic examinations, uterotubograms can be carried out in the absence of active infection to establish patency of the tubes as well as defects within the uterus as shown by these radiograms. Although iodized oils are used, a newer preparation (Salpix), which is a water soluble radiopaque medium composed of polyvinylpyrrolidone with sodium acetrizoate, apparently causes no evidence of pelvic irritation and is tolerated well. In contrast to iodized oils which are frequently trapped at constricted points in the tubal lumen and may thus cause a foreign body reaction, this newer preparation is absorbed within two hours and obviates the necessity of taking a flat film of the pelvis twenty-four hours after the use of the iodized oils. Carbon dioxide insufflations may be performed at monthly intervals if the uterotubograms fail to show evidence of patency or evidence of some partial obstruction within the tubes. On occasion it is desirable to repeat the uterotubograms, especially after repeated insufflations, to note what progress has been made.

HUHNER TEST

A Huhner test is an especially valuable procedure and in those instances in which an active number of sperm cells of normal viability are found in the vaginal and endocervical secretions, there is no need to subject the male partner to further investigative procedures. The Huhner test which consists of having the female partner report to the physician's office an hour or so after intercourse wearing an external Kotex pad should be performed at the mid

stances since the vaginal pH is about 4.5 and this degree of acidity is too high to favor sperm survival for any length of time. Vaginal infections usually produce an elevation of the pH to more alkaline proportions and accordingly do not contribute to diminished fertility on the basis of acidity.

Cervical secretions, however, are often a cause of sterility. Antibiotics may be indicated in certain types of cervicitis, but such procedures as extensive cauterization may cause irreparable damage by destroying the cervical glands. Following a dilatation and curettage, the patient should return to make sure that no stenosis has resulted since this tends to cause inadequate drainage and subsequent reinfection.

CONGENITAL MALFORMATIONS AND PELVIC INFLAMMATORY DISEASE

It is desirable even with normal menstruation present to explore the possibility of congenital malformation of the uterus such as bicornate uterus, hypoplasia, endometritis, fibroids, endometrial polyps or endometriosis. In the presence of a normal physical examination this is conveniently accomplished at the time of the uterotubogram which should be performed approximately four days after the last day of her period.

UTEROTUBOGRAMS

Any past pelvic inflammatory disease is an important cause of sterility or infertility in the female and aside

Factors interfering with this test may be obtained from the female partner and may reveal that there has been inadequate penetration of the male organ, premature ejaculation, marked postcoital leakage of the seminal fluid or perhaps dyspareunia. In those cases in which sperm cells are consistently found in the vaginal pool but not in the endocervical secretions, the uterus may be posterior with the cervix not in contact with the vaginal pool and a change in position at the time of intercourse should be suggested first in an effort to correct this difficulty. Although the hostile environment of the normal vagina is offset to a considerable extent by the buffering capacity of the semen, the sperm cells must come in contact with the cervical secretions within a reasonably short interval to permit effective sperm migration.

If a semen analysis has not been submitted and if only a few abnormal sperm cells or a low survival rate is noted in the cervical and vaginal secretions, the husband will be found at fault in the majority of instances.

OVULATION AND CONCEPTION

During the ovulatory phase, viable sperm can generally be found in the cervical canal for as long as twenty-four to forty-eight hours. The viability for fertilizing effect, however, is unknown. Although some feel that the temperature charts are not a true index of the exact time of ovulation, sperm cells are generally considered to be capable of fertilization for approximately eighteen hours

cycle when the cervical secretions are most favorable and after the uterotubogram or carbon dioxide insufflation has been accomplished. The cervix is exposed by means of a nonlubricated bivalve speculum, wiped dry with gauze and the mucus which is aspirated from the lower portion of the endocervical canal by means of a cannula attached to a 50 cc. Luer-Lok syringe, is placed on a glass slide. A second sample is obtained from the vaginal pool, deposited on the opposite end of the slide and both specimens are covered with the usual cover slip. Both specimens are immediately studied under the microscope for number, motility and morphology of spermatozoa as well as any abnormal cells or evidence of infection. This test determines whether or not the sperm cells have been properly deposited at the time of intercourse and their capability of migration within the female genital tract. If normal motility was present in the semen analysis and an absence of sperm cells in the cervical canal or sluggish activity of the sperm cells within the cervical secretion is present, with the sperm cells more active in the relatively hostile vaginal secretions, the cervical mucus must be hostile to the sperm cells. This is usually due to endocervical infection with relative stenosis or due to inadequate estrogenic levels and a hypoplastic uterus. Normally, the endocervical secretions should contain at least ten and usually fifteen to twenty-five lively sperm cells of normal morphology per high power field. In the vaginal secretions or vaginal pool, at least 20 per cent of the sperm cells should be actively motile two hours after intercourse.

Factors interfering with this test may be obtained from the female partner and may reveal that there has been inadequate penetration of the male organ, premature ejaculation, marked postcoital leakage of the seminal fluid or perhaps dyspareunia. In those cases in which sperm cells are consistently found in the vaginal pool but not in the endocervical secretions, the uterus may be posterior with the cervix not in contact with the vaginal pool and a change in position at the time of intercourse should be suggested first in an effort to correct this difficulty. Although the hostile environment of the normal vagina is offset to a considerable extent by the buffering capacity of the semen, the sperm cells must come in contact with the cervical secretions within a reasonably short interval to permit effective sperm migration.

If a semen analysis has not been submitted and if only a few abnormal sperm cells or a low survival rate is noted in the cervical and vaginal secretions, the husband will be found at fault in the majority of instances.

OVULATION AND CONCEPTION

During the ovulatory phase, viable sperm can generally be found in the cervical canal for as long as twenty-four to forty-eight hours. The viability for fertilizing effect, however, is unknown. Although some feel that the temperature charts are not a true index of the exact time of ovulation, sperm cells are generally considered to be capable of fertilization for approximately eighteen hours

cycle when the cervical secretions are most favorable and after the uterotubogram or carbon dioxide insufflation has been accomplished. The cervix is exposed by means of a nonlubricated bivalve speculum, wiped dry with gauze and the mucus which is aspirated from the lower portion of the endocervical canal by means of a cannula attached to a 50 cc. Luer-Lok syringe, is placed on a glass slide. A second sample is obtained from the vaginal pool, deposited on the opposite end of the slide and both specimens are covered with the usual cover slip. Both specimens are immediately studied under the microscope for number, motility and morphology of spermatozoa as well as any abnormal cells or evidence of infection. This test determines whether or not the sperm cells have been properly deposited at the time of intercourse and their capability of migration within the female genital tract. If normal motility was present in the semen analysis and an absence of sperm cells in the cervical canal or sluggish activity of the sperm cells within the cervical secretion is present, with the sperm cells more active in the relatively hostile vaginal secretions, the cervical mucus must be hostile to the sperm cells. This is usually due to endocervical infection with relative stenosis or due to inadequate estrogenic levels and a hypoplastic uterus. Normally, the endocervical secretions should contain at least ten and usually fifteen to twenty-five lively sperm cells of normal morphology per high power field. In the vaginal secretions or vaginal pool, at least 20 per cent of the sperm cells should be actively motile two hours after intercourse.

only one out of approximately 100,000 sperm reach the site of fertilization in the fallopian tubes.

SURGICAL CORRECTION OF ABNORMALITIES

Surgery upon such abnormalities that may show up can be undertaken but the results will depend upon the operative findings and skill of the surgeon, and in the case of tubal disease on the extent of damage as evidenced by *the uterotubograms, as well as the apparent site of obstruction.* The usual procedure is a vertical salpingostomy with resection of the obstructed portions of the tube by a circular and slightly oblique incision followed by an eversion of the lips of the new ostium and a fastening of the mucosa to the serosa by three or four fine sutures. Since this is a meticulous procedure, ophthalmologic instruments are often used. Although subsequent tube tests may show 30 to 35 per cent of the operated tubes remaining patent, the reports of resulting pregnancies after salpingostomy in the vicinity of 15 or 16 per cent represent the best statistics in the hands of specialists. When such a procedure is contemplated the couple should be warned of the technical difficulties involved since the chances of a successful outcome are probably no higher than 8 to 10 per cent in skilled hands. In those cases with total occlusion of the fallopian tubes, the results of implantation operations involving the insertion of polyethylene tubes through the resected cornu of the uterus should be watched with interest.

and may remain viable in the female genital tract for three days while the fertilizing life of the ovum has been estimated to be as long as eighteen to twenty-four hours. In some instances where conception takes place, there may be unknown variables in fertilizing potential of ova and/or sperm cells which make it difficult to correlate the estimated time of ovulation with the time of coitus. However, since the majority of fertile women with regular periods and no fear of a subsequent pregnancy have easily read temperature charts but on occasion may conceive within two to three days of the thermal shift, such instances may be an index of germ cell viability for that couple with the temperature chart revealing the time of ovulation. Although miscalculations may be eliminated by careful artificial insemination experiments, the anxiety often associated with the taking of temperature graphs and the anticipation of an otherwise impossible conception are uncontrollable factors which may produce an irregular temperature pattern and in some instances may be a reflection of the many complex psychic factors interfering with ovulation

The union of the sperm and ovum is believed to take place in the fallopian tube near the junction of the distal and middle thirds. In electron microscopic studies, the sperm heads would appear to have a small cup-like area which may possibly be a significant point of contact for the sperm and ovum. Despite the large number of sperm cells in the semen, it is interesting to note that serial sections of the tubes after insemination have shown that

puncturing of the remaining cysts may allow ovulation to take place and hence pregnancy to occur.

HORMONAL THERAPY

Hormonal therapy for sterility in the female, except for the use of stilbestrol in endometriosis and perhaps for mild degrees of hypo-ovarianism or a mildly hypoplastic uterus with inadequate cervical secretions, is not likely to be effective unless some gross endocrine disturbance has been found, such as thyroid deficiency or perhaps pituitary tumor, in which instance the primary disorder should be treated in the hope that pregnancy will result. In rare instances of chromophobe tumor in which the gonadotropic factors are not involved and in acromegaly, pregnancies have been reported.

When the female partner's periods are somewhat irregular and the premenstrual endometrium shows a weakened estrogenic effect, the cyclic administration of small doses of estrogen or perhaps 0.1 mg. of stilbestrol twice a day for twenty-four consecutive days and 10 mg. of oral progesterone from the fourteenth through the twenty-fourth day of this substitution program would appear to be definitely beneficial in helping at least some of these patients to become pregnant.

In women with unfavorable cervical secretions not due to infection, a small dose of estrogenic therapy equivalent to 0.1 mg. of stilbestrol daily, starting on the first day of the period and continuing this for twenty-four days, may objectively improve the cervical secretions as evidenced by subsequent Huhner tests.

SELECTIVE UTEROTUBAL DENERVATION

Transection of the sympathetic and parasympathetic fibers of Frankenhäuser's plexus by division of the utero-sacral ligaments through an incision in the posterior fornix of the vagina to denervate selectively the cervix, fundus of the uterus and proximal portion of the tubes is said to diminish uterine irritability, relieve tubospasm but eliminate autonomic neurovascular imbalance and in selected cases, permit a high percentage of normal pregnancies and apparently lessen the tendency of recurrent tubal pregnancy, neurogenic abortion and placental separation in other instances (Doyle, 1954).

ENDOMETRIOSIS

Other diseases of the female genital organs may be found, such as single, large retention cysts or benign ovarian tumors, as well as endometriosis. If the latter is preventing pregnancy, it is worth while to try stilbestrol for a period of months on the chance that fertility may improve. Surgical procedures for endometriosis may or may not be helpful but may be carried out when the degree of disability and the desire for pregnancy warrant them since the results in some instances are gratifying when the endometriosis is not too extensive.

STEIN-LEVENTHAL SYNDROME

In regard to polycystic ovaries such as described in the Stein-Leventhal syndrome, wedge-shaped resections with

The prompt treatment of orchitis associated with mumps in the postpuberal male by estrogenic or cortisone therapy would appear significant since the incidence of orchitis complicating mumps has been computed to be about 20 per cent. Since estrogenic hormones temporarily suppress or counteract a potential orchitis in males after puberty, 1 mg. of stilbestrol three or four times a day for at least seven days should be administered. This program has been found to reduce the incidence of orchitis from 16 or 17 per cent to 3 or 4 per cent. Similar results may be reported from the use of cortisone. Since the detrimental effects of this type of orchitis are prone to be lasting, this reduction in the incidence of orchitis accompanying mumps should be considered quite impressive.

Although the wearing of constrictive clothing which may place the scrotum closer to the abdominal wall and increase the testicular temperature, particularly in those individuals who do clerical work with much sitting, is another contributing factor for which there is no statistical proof, the avoidance of this type of clothing, such as jockey shorts, would appear to be logical and this suggestion should cause no undue hardship to the male partner.

There is little to be done in regard to oligospermia or abnormal forms of spermatozoa unless there is a gross endocrine disorder which, in most instances, is unlikely. The so-called testosterone rebound phenomenon following the injection of large doses of testosterone propionate (50 mg. intramuscularly per day) or depo-testosterone

TREATMENT OF THE MALE

The treatment of male infertility of appreciable degree is disappointing. Although spontaneous variations with improvement may occur in some instances, the mechanisms involved are not clear and although many so-called contributing factors are often stressed as important in male sterility, many of these factors would appear to be a matter of personal opinion or conjecture rather than established facts based on scientific proof or conclusive statistical data, since the presence of these same factors in an appreciable number of highly fertile males has no apparent detrimental effect. Other than the improvement of general health measures which should be advised for any patient when indicated, there are a few measures from a prophylactic standpoint which would appear worthy of consideration, such as when the male should change his work because of constant contact with some chemical or other substance known to have a detrimental effect on the seminiferous tubules. Since the incidence of epididymitis following specific and nonspecific urethritis has fallen from approximately 15 to 2 per cent since the institution of antibiotic therapy, the prompt institution of adequate therapy to reduce the incidence of obstructive oligospermia and azoospermia, and the referral of the patient to a genitourinary specialist rather than tend to rely on antibiotics for a prolonged period when there is a persistence or recurrence of a urethral discharge would appear important.

CHAPTER VIII

GYNECOMASTIA

Gynecomastia is enlargement of the breasts in the male and may be due to increase in ductal tissue or in the *periductal fatty tissue and sometimes to an increase in* fibrous tissue. The incidence of gynecomastia ranges from about 8 to 16 per cent per 100,000 men who are admitted to the hospital in the Army and Navy.

Enlargement of one breast or both may occur almost any time before puberty. The reason is often unknown and it is likely to subside. Such enlargement is often referred to as mastitis, although evidence for inflammatory changes is scanty.

With the onset of puberty in many boys there is often enlargement of the breasts, also enlargement of the areolae and the nipple. This causes great concern. If the boy is obese, the prominence of the breasts is greater. In many instances, this pubescent enlargement of the breasts disappears during adolescence and before maturity; on the other hand, it may not.

The theory of androgen and estrogen imbalance as the

(400 to 600 mg. per week) *is not generally considered* to be effective. It is stated that the injection of such large amounts of testosterone should be continued until the formation of spermatozoa is completely suppressed. A rebound should occur after eighteen or twenty weeks, at which time the semen should show greater numbers of spermatozoa. In the author's experience there have been only 2 cases in which the rebound seemed likely but could not be proved.

Mention has been made in the section under "Eunuchoidism" that in a rare instance, in fact in 3 instances in our experience, spermatogenesis and fertility followed the use of testosterone alone (in one case) and testosterone and chorionic gonadotropin (in 2 others).

A few reports since the publication of that observation have confirmed that finding. The rarity of this occurrence suggests that it may well have been a very late puberty occurring after the age of 22 or 23, but certain observations on these patients tend to disprove that this was the case.

It may definitely be stated that if the testes of the eunuchoid male increase in size upon the administration of relatively large amounts of testosterone (20 to 30 mg. orally daily), 25 to 50 mg. of testosterone propionate weekly or 100 mg. of depo-testosterone every two weeks, fertility in all probability will result. On the other hand, if there is no increase in the testes, fertility is certainly not likely to come about. In the cases in which fertility did occur, there was an increase in the growth of the testes.

ment of one or both breasts which is tender and, as stated before, this is referred to as mastalgia. The treatment for this is not too satisfactory. Occasionally the tenderness seems to decrease after administration of testosterone orally in doses of 10 to 30 mg. daily. Cancer of the breast may occur in men.

True hermaphroditism or pseudohermaphroditism in the male might be responsible for gynecomastia. True hermaphroditism is bisexuality in which there is a distinct ovary and distinct testis in the same individual, or there may be ovo-testes present with enlargement of the breasts with very little secretion of male sex hormone. In true adrenocortical hyperplasia or adrenogenital syndrome in the male I know of no case reported in which there has been enlargement of the breasts, but theoretically this could occur if the predominance of the adrenocortical secretions were estrogens.

Gynecomastia is occasionally seen in eunuchoids and in Klinefelter's syndrome This syndrome is described elsewhere and is characterized by an appearance of masculinity, save for gynecomastia, and normal sex interest and potentia The testes are smaller than normal and no sperms are found. The breasts are enlarged, the enlargement consisting of a predominance of fibrous tissue, although duct development is somewhat increased. The areolae are apt to be pigmented. The characteristic urinary finding is an excess of follicular stimulating hormone (tubular stimulating hormone) to the degree found in castrates or in women in the menopause.

The suspicion of malignant tumor causing gynecomas-

cause of gynecomastia, in which the amount of estrogen which is present in all males overbalances the androgen, is inconclusive as regards idiopathic varieties.

No true mammogenic hormones have been isolated in humans, but these are known to occur or to be found in the pituitaries of cattle.

When one considers the possible etiology of gynecomastia in males, the liver must be taken into consideration because it breaks down and conjugates estrogens. In cirrhosis of the liver the naturally occurring estrogens in the male may not be metabolized, causing enlargement of the breasts along with testicular atrophy. Malnutrition which affects the liver may also render it unable to metabolize properly estrogenic substances and give rise to gynecomastia. This has been noted especially when the patient is overcoming the malnutrition and the breasts appear to gain in size more rapidly.

There are estrogen producing tumors in males, such as adrenocortical carcinoma which is the most common cause of gynecomastia and feminization when due to tumor. Less than 20 such cases have been reported in medical literature. Here, as in cirrhosis of the liver, there is also atrophy of the testes due to the inhibiting effect of excess of active estrogen upon the pituitary gonadotropins which normally maintain the testes.

There then also must be some hereditary factors present or variation in the end organ response, for men with gynecomastia are occasionally seen without any other evidence of endocrine disorder.

At any time during the male life there may be enlarge-

CHAPTER IX

HIRSUTISM AND PROCEDURES FOR INVESTIGATION

Hirsutism is one of the most frequent conditions considered to be of endocrine origin and one for which many women, especially in the younger age groups, seek advice.

The appearance of hair in the female in those regions which are normally hirsute in the male may be considered abnormal, at least should be presumed so until all possible causes are reasonably ruled out. When the female is brunette, any excess hair growth is more noticeable. It is not very often that a blonde hirsute woman seeks medical advice, at least in comparison to the number of brunettes seen.

There appears to be a great tendency for hirsutism to be familial or racial in origin. There are certain epochs in which hirsutism becomes apparent, namely, menarche,

tia is to be aroused in the recent development of bilateral breast enlargement in adults rather than a long history of its existence. Treatment of prostatic cancer with estrogens causes breast enlargement and in a few cases cancer has been found in the breasts. Whether this is metastatic carcinoma of the prostate or primary mammary cancer is not settled. The administration of methyltestosterone or even chorionic gonadotropin may cause gynecomastia.

Treatment of gynecomastia in the male is entirely one of various types of plastic surgery when desired.

certainly is a curious situation, particularly when one considers that the beard is continuous with head hair.

Axillary and pubic hair in the female is caused by adrenocortical hormones; the pubic escutcheon in general is different from that of the male. In hirsute women it takes on the male pattern, yet in simple hirsutism there is no further tendency toward masculinization. This suggests, therefore, that certain hormones can cause excessive hair growth but are limited in their effects as regards other changes toward masculinization.

Hirsutism has been noted in several cretins, both male and female, and in one case of adult myxedema, which disappeared on treatment with desiccated thyroid. The 17-ketosteroid excretion in these cases was not increased; in general these metabolites are decreased in thyroid deficiency. The reason for hirsutism in these cases is particularly obscure, since most cases tend to have less body hair as well as head hair. These examples are given here to show that there is still much to be learned about hair growth.

The mental reaction of women to acquiring hirsutism varies greatly. Some whom I have seen have finally resorted to shaving and are no longer too concerned, while others are in a state of great anxiety and unhappiness, at times being mentally unbalanced. The average girl, however, is deeply concerned and is entitled to a careful history and physical examination, even though the chances are poor that an abnormal endocrine state (other than hirsutism alone) will be found.

pregnancy, menopause, although I have seen rather marked hirsutism in childhood without obvious cause. Newborn babies may be quite hirsute, which soon disappears. Because of these phenomena and because hirsutism is associated with certain endocrine disorders, one must assume that there is a hormonal stimulus to hair growth. Do some people have more hair buds than others, or is there a congenitally greater hormonal secretion in some? Is hirsutism in the female a sign of early masculinization, or are there hormones which stimulate hair growth without causing further signs of masculinization, for example, a weak androgen or a strong androgen? These are some of the unknown features in relation to the clinical problem of hirsutism.

Testosterone when given to females will cause hirsutism, but it is well known that some women have a more pronounced reaction than others. Testosterone will also lower the voice and enlarge the clitoris if given long enough and in sufficient dosage. Cortisone will cause some degree of hair growth but not the other features of true masculinization. Some believe that cortisone and hydrocortisone are converted into weak androgens and produce hair in this way In acromegaly, hirsutism may occur. Is this due to growth hormone or excess androgens from the adrenal cortex?

In patients with advanced hypopituitarism who have greatly decreased adrenocortical hormones, there may be almost complete absence of facial, axillary, pubic and body hair, without change in head or eyebrow hair. This

In arrhenoblastoma the 17-ketosteroid excretion may not be elevated. The pattern of steroid secretion might very well determine the presence of increased androsterone or dehydroisoandrosterone, but these are not usually available for routine laboratories in general hospitals. The same also holds true in the Stein-Leventhal syndrome in which 17-ketosteroids vary considerably, so that one cannot exclude these diseases by such determination.

If there is sufficient reason in view of the foregoing to investigate the situation further, the patient should have a pelvic examination under anesthesia and if this is negative, presacral air injection for adrenal tumor or hyperplasia. Laparotomy may be justified in many cases if the above examinations are inconclusive.

One of the reasons for determining the 17-ketosteroids is that if values of over 50 mg. are found, there is justification for further investigation as just outlined, but it is not uncommon to find values from 20 to 50 mg. in simple hirsutism. Then again it is well to have a record of the 17-ketosteroid excretion for comparison to an analysis, say three to six months later; if there is a consistent rise in the total amount excreted, greater suspicion of tumor is to be entertained.

In one case of arrhenoblastoma in a 16 year old girl with hirsutism and amenorrhea of eight months duration, the 17-ketosteroid excretion was only 16 mg. and 20 mg. in two twenty-four hour specimens, which is perfectly normal, and in another patient with adrenocortical tumor with amenorrhea of only two months duration the value was over 150 mg per twenty-four hours, which was

In taking the history, the onset and duration are fairly important to determine. For example, recent onset unrelated to the epochs mentioned above, should attract more attention than hirsutism of several or more years duration when unaccompanied by any other symptoms or physical change.

In addition there may be a mild plethoric appearance and an increase in strength and endurance, although the latter is not often mentioned by the patient unless specifically sought in the history taking.

If the patient has not yet reached the usual age for epiphysial closure, the bones may be x-rayed to determine an advanced bone age. For example, should the epiphyses be closed at the age of 15 with other suggestive signs or symptoms, it would point to increased secretion of androgenic hormones.

A twenty-four hour urine specimen should then be collected for 17-ketosteroid determination. There are no other routine laboratory tests which will in any way help in the detection of an androgenic type of tumor. There is one exception to this statement, namely, Cushing's disease, and the differential diagnosis can be determined by the laboratory investigations under that heading.

The types of tumor or the types of hyperfunction to be considered in hirsutism are as follows: (1) familial or racial hirsutism, (2) adrenocortical tumor, (3) adrenocortical hyperplasia, (4) Cushing's disease, (5) arrhenoblastoma, (6) adrenal-like tumor of the ovary, (7) Stein-Leventhal syndrome, (8) acromegaly, (9) thyroid deficiency.

CHAPTER X

STEROID AND OTHER HORMONES IN GENERAL PRACTICE

Steroid compounds, whether they be the actual hormones secreted by endocrine glands or not, include estrogens, progesterone, testosterone, cortisone and hydrocortisone. Corticotropin (ACTH) is the pituitary hormone capable of stimulating the adrenal cortex to produce and secrete cortisone-like substances and perhaps other hormones of less clinical significance. Chorionic gonadotropins derived from the urine of pregnant women simulate the gonadotropins of the pituitary (hence the name APL, meaning anterior pituitary-like) and are capable of stimulating and perhaps developing (from fibroblasts) the Leydig cells of the testes, producing testosterone. •

The widespread use of the steroid compounds has come about through their pharmacologic effects rather than through replacement therapy in glandular deficiencies.

unexpected in view of the scant evidence of masculinization. Thus it can be seen that the 17-ketosteroid excretion may be revealing in one instance and not in another.

The treatment of tumors which cause hirsutism is surgical. One must not expect the hair to fall out as soon as the tumor is removed, in fact, there is no great tendency for it to do so, but, however, new hair growth does not take place. The hair about the breasts and abdomen seems to decrease first, but the number of cases so encountered are so few that statistical analysis of hair loss is not possible.

It is well to mention here that there may be certain tumors which produce a combined picture of Cushing's disease and masculinization. When one encounters a combined picture of Cushing's disease and virilization, a likely diagnosis is malignant type of tumor of the adrenal cortex, although the degree of malignancy may not be great and excision may cure the patient.

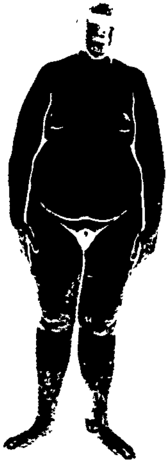


Fig 16 Klinefelter's syndrome This condition is characterized by gynecomastia, testicular atrophy and excess FSH in the urine. Histology of testes is one of loss or hyalinization of seminiferous tubules Leydig cells are often not decreased and sexual function is often normal The genitalia here look underdeveloped, but the shaft of the penis is hidden by fat. All these features were present in this case

With the exception of the estrogens, substitution treatment for comparatively rare diseases such as Addison's disease, hypopituitarism or even hypogonadism in the male would probably not have been possible for years since the cost of these compounds, especially cortisone and corticotropin, would have been prohibitive for reasons to be mentioned. Collip's recovery of corticotropin (ACTH) fifteen years or so before its large scale commercial preparation or Kendall's isolation of compound E (cortisone) from beef adrenals in as many years represents the state of affairs which still might be present today save for the impetus given both preparations by their remarkable effects on rheumatoid arthritis. The decision to make cortisone (and other adrenal compounds), which apparently was a high priority project of the Government during the war, came about on what later proved to be a false rumor, namely, that Germany was administering adrenal compounds to their fighter pilots for the purpose of increasing their effectiveness in one manner or another. Furthermore, the financial gamble to carry on the work by a private concern is no less remarkable in view of what appeared to be a limited market at best. Thus, patients in whom these compounds act as substitution therapy reaped the benefit indirectly.

CORTISONE AND HYDROCORTISONE

The use of these compounds as substitution therapy is dealt with in the chapters on adrenal and pituitary dis-

ease. The relatively small doses required for this purpose contrast with the larger doses needed for pharmacologic effects.

In addition to their use in replacement therapy these compounds are also used to inhibit other glandular secretions. In this connection it is pertinent to point out here that administered cortisone (which is probably converted to hydrocortisone by the liver) and hydrocortisone depress *the pituitary secretion of corticotropin (ACTH)* which under normal conditions is responsible for the stimulation of the adrenal cortex to secrete hydrocortisone. The latter is considered to be the chief compound of this type to be elaborated by the adrenal cortex, rather than cortisone. Thus, after prolonged cortisone or hydrocortisone therapy for almost any disease, the adrenals atrophy, producing little or no hormone themselves. This should always be borne in mind, because a real danger exists and fatalities have resulted when patients have undergone some rather severe stress without active adrenals of their own. In such cases the continued administration of cortisone, or even better, a doubling or tripling of the previous dose had it been known, would have prevented such tragedies. For this reason all cortisone users should be warned about this possibility and should undoubtedly carry cards indicating the amount of cortisone or hydrocortisone used daily, for what it is being used and instructions to double or triple the dose at times of stress, i.e., acute febrile disease, accidents, burns or operations.

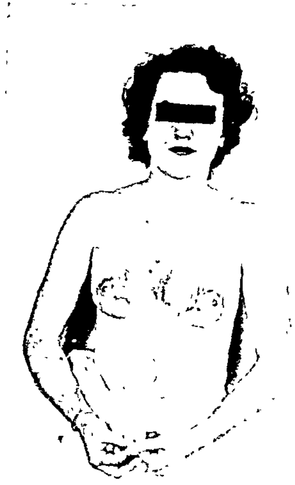


Fig 17. Hirsutism A 25 year old female with complaint of hirsutism beginning at time of menarche, increasing particularly in past few years. Normal regular catamenia No voice change or enlargement of clitoris Twenty-four hour 17-ketosteroids 40.3 mg Exploration advised. Three years later, at which time the clitoris had become enlarged, an encapsulated adrenocortical carcinoma was removed at another hospital Objective improvement reported slow. The relationship between early hirsutism and later development of tumor is difficult to determine

once cortisone is reduced or omitted—a happy (or unhappy?) medium must be worked out.

Rheumatoid arthritis has its own unpredictable relapse and remissions. Perhaps some of the remissions induced by cortisone would have occurred without cortisone, but at least these patients were comfortable until the remission took place. This may be a legitimate argument for using cortisone in the earlier cases—at least in my own experience the longest or complete remissions were as a rule those with the shorter durations before therapy. I do not believe this is a universal experience or that it can be proved statistically.

Many plans of treatment have been carried out by different observers for the treatment of rheumatoid arthritis with cortisone. As stated before, the continual administration of 100 mg. or more for weeks to months is no longer generally advised The use of 100 mg. a day for several weeks, gradually reducing the dose to 15 or 25 mg. a day, is frequently recommended. The plan of treatment consists of initial doses of 50 mg. a day, increasing the amount to a suppressive dose of around 100 to 150 mg. and then reducing the dose slowly over a period of several weeks, then discontinuing it for one or two months. During this time, aspirin in full dosages of from 80 to 100 mg. a day should be given if tolerated. Still another method is to begin with a small dose as mentioned above in an attempt to determine the most effective dose, that is, the lowest dose allowing the patient to be reasonably comfortable and continuing this dose for several months.

Cortisone and hydrocortisone now permit total adrenalectomy for whatever purpose it is performed. From the endocrine standpoint, adrenal insufficiency from surgical procedures need no longer be feared, as most patients with no adrenals whatsoever can live on 25 to 50 mg. of cortisone daily in addition to desoxycorticosterone acetate which, however, is not needed in all cases.

First of importance for the nonendocrine uses of cortisone and hydrocortisone is rheumatoid arthritis. Most writers agree that cortisone should not be the first treatment to be used in every case. Indications are certainly not standardized, neither is the dosage. The original method of giving 300 mg. a day and then gradually reducing it to around 100 mg. a day is not often used. These larger doses certainly give marked relief and a wonderful sense of well-being, but why let the patient taste such dramatic relief if it cannot be maintained? There is much to be said for beginning with a small dose combined with large doses of aspirin and working up to not over 75 mg. a day. Even this amount should probably not be maintained but only used on days when symptoms break through the cortisone barrier.

One objective in the treatment of arthritis is the prevention of deformities. Exercises either active or passive are not well borne in some cases and nothing permits a wider range of joint motion than cortisone. Much can be accomplished during a few weeks of higher cortisone dosages in this regard. There is no question that in some cases the improvement in range of motion may revert

effects in continuing hormonal therapy which was in general on moderately low dosage schedule, were not as marked as the lay public is led to believe.

The response to patients with cortisone or ACTH is unpredictable. One may find a decrease in the sedimentation rate without corresponding clinical symptoms and one may have improvement of clinical symptoms without a marked change in the sedimentation rate. The appearance of side effects or complications of cortisone also follows no definite pattern.

Perhaps it is well to attempt in a general way the differentiation between the side effects of cortisone and ACTH and complications. Of the side effects commonly noted are facial rounding, fluid retention, slight hirsutism, acne, menstrual disorders and weight gain. These side effects are not particularly serious and may be reversed by decreasing the amount of cortisone given. When the daily dose is over 75 mg. it is stated that the side effects are three times as great as those receiving doses under 75 mg. a day. Of the more serious side effects, or shall we say complications, the mental disturbances, sometimes of alarming degree, may occur in 20 per cent or more, increase of blood pressure in a few cases, ecchymosis and easy bruising in a small number, and thrombophlebitis in a still smaller number of patients. Aggravation of peptic ulcer is reported in a small number of instances, osteoporosis in still fewer. In addition, there are reported such disturbances as increase in sweating, aggravation of menopausal symptoms, decrease in resist-

After several months of cortisone therapy, it is the practice of some to use corticotropin in gel, to restimulate the adrenal cortices to prevent atrophy, for a period of several more months. The dose of this preparation again has to be found out by trial and error. Amounts up to 20 or 30 units daily or every other day should cause a reasonable improvement, following which the dose can be reduced to 5 or 10 units every other day. After several months of this, cortisone may be resumed.

When corticotropin is withdrawn there may be a period of relative adrenocortical insufficiency due to inhibition of the patient's own pituitary as regards corticotropin *secretion. There is less likely to be a serious deficiency if* corticotropin is reduced to a small dose instead of stopping it suddenly when high dosage is being used.

According to Hench and Ward of the Mayo Clinic who summarized the results of prolonged hormonal treatment of rheumatoid arthritis from various published reports of 216 patients who initiated the treatment, 166 were still continuing treatment, or 77 per cent. Complete symptomatic relief on continuing hormonal treatment occurred in 17 per cent, marked improvement 34 per cent, moderate 20 per cent, slight 5 per cent, and little or none in 1 per cent.

The reasons for discontinuing this type of treatment were approximately as follows: clinical result unsatisfactory in 10 to 15 per cent; undesirable effects of complications in 10 per cent; further treatment unnecessary in 5 to 10 per cent. Thus it can be seen that the undesirable

cortex, such as weakness, lassitude, exhaustion, possible fever and anorexia, and if severe, may lead to abdominal symptoms, namely, diarrhea, vomiting, nausea. The duration of symptoms related to adrenocortical insufficiency naturally, *of course, depends upon the degree of suppression* which has occurred and this may take weeks to months before recovery takes place.

There are certain musculoskeletal reactions which occur upon withdrawal of cortisone or ACTH which are to be *distinguished from a flare-up of the rheumatoid state.*

These symptoms are not associated with swelling and redness of the joints as might be expected in a flare-up of rheumatoid arthritis, but are described by Slocumb as the symptoms simulating arthritic symptoms as a result of excessive cortisone administration. These symptoms consist of aching of the muscles and joints, often diffuse, rather than joint pains themselves, associated also with fatigability and weakness and emotional instability. Little help comes from the usual methods of treatment such as physical therapy, heat or salicylates, and symptoms resembling those of psychogenic rheumatism The patient is hypersensitive and cannot stand digital pressure, the symptoms appearing out of proportion to the objective evidence of synovitis; it tends to be psychic in nature and increasing of the cortisone may temporarily help the fatigue and aches but increases the psychic and emotional symptoms. The only method of controlling this is to decrease the cortisone gradually over a period of three to four months.

ance to infection, headache, weakness and low serum potassium, striae of the skin, and so on.

In addition to the amount of cortisone or ACTH taken daily, the duration of treatment also has some bearing on the side effects. Perhaps the most serious complication *or effect of cortisone is the depression of the pituitary* adrenal cortex mechanism, which was discussed in the beginning of this section.

Certain precautions can be observed during the treatment with cortisone, hydrocortisone or ACTH: a restriction of the intake of sodium to about a gram a day and the use of potassium chloride to counteract any potassium depletion and also, perhaps, as a diuretic. Sedation for mild mental stimulation can be prescribed. Insulin will probably have to be increased in case of a question of diabetes mellitus. In this connection it might be well to point out that at the present time any appearance of diabetes during therapy for rheumatoid arthritis with these preparations probably indicates a latent diabetes rather than one caused by the use of cortisone. Acute infections may be somewhat masked by the use of cortisone, and antibiotics should be used should such infections develop. Certain symptoms should be watched for upon discontinuing cortisone. Certainly if cortisone has been given for a long time in fairly large doses, its withdrawal should not be sudden but gradual. The symptoms which may occur upon withdrawal may be related to a return of the rheumatic condition, such as stiffness, pain and swelling, or they may be related to the depression of the adrenal

cluding myocardial insufficiency, hypertension and a tendency to thrombotic or thrombo-embolic phenomena, also any convulsive disorder.

(For the intra-articular use of hydrocortisone, see below.)

TREATMENT OF RHEUMATIC FEVER

The effect of cortisone on acute rheumatic fever is striking. In fact, the improvement, particularly in the critically ill children, was so dramatic when first used it seemed certain that here was an agent which surpassed any previous therapy. Yet all agree that in all probability cortisone or corticotropin does not influence the course of the disease. Neither has it been definitely proven that it prevents valvulitis. In a preliminary report on a special study set up by the Council on Rheumatic Fever of the American Heart Association and the British Medical Research Council, it was stated that there is no systematic pattern in the way cortisone, corticotropin or salicylates might affect individual symptoms, signs or laboratory observations.

In children who are critically ill, the rapidity with which cortisone works appears to be actually life saving. In some instances, cortisone has a more rapid effect than salicylates. In other cases, apparently the course of improvement may run parallel.

The effects of cortisone upon active rheumatic fever and active rheumatic carditis may be classified accord-

Retreatment for pituitary adrenocortical insufficiency with cortisone or corticotropin may have to be resorted to but it only prolongs the final recovery of the pituitary or the adrenal cortex to function normally.

A more reasonable view is now held in regard to the use of these preparations in the treatment of rheumatoid arthritis. Initially there was great enthusiasm, then finally great disappointment and adverse reaction to their usage, but hormonal therapy is a practical office procedure if a reasonable familiarity with effects of the hormone in the disease is acquired. Careful selection of patients, careful management, reducing the dosage when side effects are significant rather than allowing them to continue, and experience teach the physician how best to manipulate dosage in connection with other methods of treatment. It is to be remembered that these preparations are used for an active rheumatic process and not for deformities and joint fixations which do not respond to cortisone. However, in some instances it is not always possible to predict how much a joint will loosen up and range of motion be increased, either by the effect of cortisone or by the relief of pain which enables the joint to become more flexible. Generally speaking, it is accepted that certain definite contraindications exist: active tuberculosis, psychosis, Cushing's syndrome, and serious infections which cannot be readily controlled by antibiotics. Of the less serious contraindications are peptic ulcer, renal insufficiency, severe psychoses in the past, osteoporosis, diabetes, cardiovascular insufficiency, in-

sedimentation rate may be increased for one to five weeks. If such a child is being treated at home it would not seem possible to distinguish between the two, but in view of the frequency of the rebound phenomenon, it seems wise to withhold further cortisone treatment unless the patient becomes gradually much worse, indicating a true recurrence.

In milder cases of acute rheumatic fever, cortisone need not be administered; salicylates can be used with good results. Some workers apparently combine salicylates with smaller doses of cortisone than when the latter is used alone in acute cases.

It is also desirable to administer penicillin during acute rheumatic fever to rid the throat of hemolytic streptococci. This can be done by the administration of 300,000 units of penicillin G and repeated in a period of a week or two. Depo-penicillin, 600,000 units, may be given once in two weeks. Oral penicillin may be used thereafter, but with the long-acting preparations only two injections per month are required to maintain blood levels, oral therapy is probably less desirable for prophylaxis during the following year or two to prevent recurrence.

Cortisone should be given orally and be divided in three or four doses during the twenty-four hours In children it is advisable to begin with dosages of 100 to 200 mg. a day, gradually decreasing the dose. For an acutely ill child, the 300 mg. a day dosage is desirable. Duration of treatment is approximately six weeks and dosage should be regulated after the process has quieted down

ing to manifestations which are more or less nonspecific and those which are manifestations of rheumatism. Of the nonspecific signs, the temperature falls fairly rapidly, the heart rate decreases, clinical toxicity disappears, the patient looks well quickly and his appetite increases. There is a fall in the erythrocyte sedimentation rate and often an increase of hemoglobin.

Of the rheumatic manifestations, the polyarthritis subsides promptly; pericarditis if present disappears; edema when congestive failure is present subsides either spontaneously or in connection with the low salt diet; the quality of the heart sounds improves and the gallop rhythm usually disappears. Murmurs, organic or functional, may also disappear. There is a greater tendency for systolic murmurs to disappear than for aortic or mitral diastolic murmurs. The heart shadow decreases in size.

As soon as the acute phase has subsided, the dosage should be decreased and then finally discontinued. Following discontinuance of treatment, the so-called rebound phenomenon may occur within a period of a few days to two weeks. There is a recrudescence of some of the clinical and laboratory abnormalities, often fever and polyarthritis. This should not necessarily be interpreted as a recurrence of rheumatic fever and should subside without instituting further cortisone treatment. The duration of the rebound may last from one to two weeks and it is the experience of some that the rebound manifestations may be more severe than the first attack. The duration of the rebound ranges from one to two weeks, whereas the

come. To date, cortisone and corticotropin are the only really effective agents for the symptomatic control of these conditions. Sufficient amounts of cortisone or corticotropin should be used to produce an optimal effect. In acute stages of these disorders, doses of cortisone up to 500 mg. a day or 300 units of corticotropin per twenty-four hours have been required.

Corticotropin in solution may be given four times in twenty-four hours intramuscularly or, if the gel is used, about one quarter of that dose every twenty-four hours. If the patient is hospitalized and the situation demands it, 20 to 50 units can be administered intravenously in 1000 cc. of saline or glucose over a period of eight hours.

If there is a poor symptomatic response, especially with continued use, the possibility of an associated infection must be entertained and antibiotic therapy given. As in the treatment of rheumatoid arthritis or other conditions, as soon as satisfactory improvement occurs, the dose is decreased to what is felt to be a maintenance dose. Such may vary between 25 to 75 mg. of cortisone orally, or 5 to 20 units of corticotropin in gel daily or every other day. In a few, very small amounts of corticotropin in gel, such as 10 units every other day, have been sufficient to maintain some patients in remission for several years. In these diseases, as in rheumatoid arthritis, the signs and symptoms of prolonged therapy must be watched for and the decision to reduce the dose in face of further deterioration of the patient without the hormone has to be made.

to that which prevents recurrence of symptoms. Treatment should be carried out more than six weeks if there is reason to believe that the course of the disease has not run out. Retreatment should be instituted if there is a recurrence and when it is certain that the flare-up is not simply a rebound phenomenon.

During treatment the salt intake should be low, 1 gm. a day, and if there is congestive failure it should be reduced to less than 100 mg. a day. Potassium chloride in enteric-coated tablets, 1 gm. two or three times a day, should be given if the dose of cortisone exceeds 100 mg. a day.

Side effects or undesirable effects of cortisone therapy occur in patients treated with rheumatic fever as in any other case. These are enumerated under the discussion of *rheumatoid arthritis.*

OTHER COLLAGEN DISEASES

Disseminated lupus erythematosus, periarteritis nodosa, diffuse scleroderma and dermatomyositis are collagen diseases. It is not my purpose to discuss the diagnosis of these diseases but only to point out that they are often progressive, with a high mortality rate, although there is considerable variation in this regard and patients may live many years.

These diseases probably justify the use of continued cortisone or *corticotropin because of this uncertain out-*

or two injections may be necessary. In hypertrophic arthritis, continued treatment depends on the amount of relief obtained and its duration. Hydrocortisone is a valuable adjunct to the treatment of rheumatoid arthritis whether or not systemic therapy is being used with corticotropin, hydrocortisone or cortisone. Joints may be drained of fluid and 12.5 to 50 mg injected. No systemic effects occur when hydrocortisone is used only in the joints.

Acute attacks of gouty arthritis may subside quickly with the intramuscular injection of 80 to 120 or more units of corticotropin in gel or by an eight hour infusion of 25 units of corticotropin in glucose or saline. Oral cortisone in doses of 300 mg. per twenty-four hours is less effective. Colchicine is recommended as simultaneous therapy to prevent recurrence or for interval therapy, aspirin or benemid for uricosuric effect.

TREATMENT OF ASTHMA AND HAY FEVER

Cortisone has become probably one of the most effective agents for the control of asthma and rhinitis. It does not cure and its effects are temporary. Upon withdrawal of cortisone or ACTH, the symptoms will sooner or later return. The use of cortisone or ACTH should be reserved for the intractable cases which have not responded to treatment by recognized means or to carry the severely ill patient through a crisis.

A good many patients to date have been maintained on small amounts of cortisone after the initial larger doses

THE INTRABURSAL OR INTRA-ARTICULAR USE OF HYDROCORTISONE IN HYPERTROPHIC ARTHRITIS, RHEUMATOID ARTHRITIS, BURSITIS, GOUT

The intra-articular injection of hydrocortisone is an effective method in the treatment of hypertrophic arthritis associated with swelling, pain, joint fluid. The knees appear to be the most desirable joint to treat, although the hip and other joints may be injected. After suitable skin preparation, novocain may be injected, although not always necessary, and fluid removed if possible, after which 12 to 50 mg. of hydrocortisone acetate is injected. If no fluid can be obtained, the hydrocortisone is drawn up in the syringe and firm pressure applied against the plunger as the needle is directed toward the joint. When the latter has entered the joint space, using the same pressure on the plunger it will slowly give way as the hydrocortisone leaves the syringe.

Hydrocortisone may be injected into bursae with great relief. If no fluid is found, the compound is forced in more or less hit or miss, as it cannot always be determined if the needle is within the bursal sac. Acute subdeltoid, elbow and trochanteric bursae are the ones most frequently injected.

Injection of hydrocortisone directly into ganglia is said to cause them to disappear. The duration of effect is from one or a few days to several weeks. In acute subdeltoid bursitis of a few days duration it is possible that only one

titis, some cases of dermatitis medicamentosa, seborrheic dermatitis, pemphigus, nummular dermatitis, erythema multiforme, and erythema nodosum.

Treatment for skin diseases can be prescribed in a similar manner to that recommended for rheumatoid arthritis. Since certain of these skin diseases are self limited, the need for continued therapy, of course, is not necessary.

The topical use of hydrocortisone ointment has marked value in certain skin diseases and may make it unnecessary to give cortisone or corticotropin systemically. It is effective in inflamed, oozing dermatitis and ectopic dermatitis, but is not effective in a lichenified skin. It is especially helpful for pruritus vulvae or pruritus ani. Ointment with 1 or 2.5 per cent hydrocortisone is usually satisfactory.

Cortisone may be given simultaneously with penicillin in patients who are sensitized to the latter, when penicillin therapy is vitally necessary, such as in subacute bacterial endocarditis, or syphilis. It should prevent the skin manifestations in doses of 50 mg. a day.

For the acute stage of the penicillin reaction involving the skin and the mucous membranes including the tongue, cortisone systemically is excellent and hydrocortisone ointment may be applied to the tongue, relieving burning.

EYE DISEASE

Cortisone, hydrocortisone and corticotropin have a definite but a limited use in eye diseases. The most favorable

have been used for controlling the severe initial state. For the latter, cortisone is given in 200 to 300 mg. doses during the first few days and then gradually reduced. ACTH may be given intravenously in an infusion, or the gel intramuscularly, as stated previously, to control acute attacks. Some believe that it is generally more effective than cortisone.

In maintaining chronic asthmatics on cortisone, we have again the same differences of opinion as we do in the treatment of rheumatoid arthritis, namely, short courses of therapy with interruptions or continuous administration of small doses, the patient being under observation at regular intervals. Naturally, all other forms of therapy also should be used in connection with the hormones.

The contraindications of hormonal therapy are the same as in the treatment of other diseases, namely, hypertension, heart failure, pulmonary tuberculosis, an active peptic ulcer, possibly severe diabetes mellitus, and severe osteoporosis. These preparations, however, may have to be used in spite of these contraindications. In general, no permanent damage has been noted in patients using reasonable amounts of cortisone for asthma over a period of several years.

DISEASES OF THE SKIN

Cortisone and corticotropin are perhaps being used more in skin than in other diseases. Their most effective use is in severe cases of angioneurotic edema, contact derma-

Hydrocortisone also is available in an ophthalmic oint ment of 1.5 per cent. This is applied four or five times a day until the acute phase is over; then one application a day should be satisfactory.

Parenteral administration of corticotropin in intravenous infusion is rarely indicated in anterior inflammations of the eye. For the more deep-seated diseases, these may have to be used, but should be carried out under the supervision or advice of an ophthalmologist.

GASTROINTESTINAL DISEASE

Everyone using cortisone or corticotropin extensively has had the experience of observing patients with acute exacerbations of a duodenal ulcer, sometimes with hemorrhage or perforation. Blaming this on these hormones is only circumstantial evidence and does not necessarily prove cause and effect. Duodenal ulcer occurs in 4 to 5 per cent of patients with rheumatoid arthritis, so, in view of the great number of patients with this disease who are treated, it would not be unexpected to find these complications even without cortisone therapy.

Favorable results with the administration of cortisone or corticotropin have been observed in the treatment of sprue It does not cure the disease but may instigate a remission. As a result of cortisone given in doses of 20 to 100 mg daily, patients with this disease have a better appetite and feel stronger, with a disappearance of abdominal cramps and distention and a decrease in the

action of these preparations is in alleviation of inflammation and exudation of the external eye.

They are of particular value when the inflammation of the eye is the result of physical trauma, allergy such as occurs with hay fever, or infection. When due to bacterial infection it must be remembered that these agents are *not antibacterial and that other measures should be used* to combat this. Such antibiotics as bacitracin, neomycin, or sulfacetimide may be combined with cortisone in ointment. If the bacteria are not sensitive to these drugs, other antibiotics may have to be used.

Acute iritis, particularly the type associated with rheumatoid arthritis, reacts favorably to instillation of cortisone or hydrocortisone in solution, and if the attacks recur frequently, a small amount such as a drop a day may be used prophylactically over a period of time.

Degenerative diseases of the eye show little improvement with the use of these agents. If it is known that the eye condition is a result of tuberculosis, its use should not be advised.

For inflammatory conditions of the external eye, cortisone or hydrocortisone, as collyrium or in ointment, may be used. These agents are available commercially as collyrium in 0.5 per cent and 2.5 per cent solutions, roughly equivalent to 25 mg. per 1 cc. Several drops are administered every one or two hours during the acute stages of inflammation until a satisfactory response occurs; thereafter one or two drops during twenty-four hours may be sufficient to maintain the improvement.

Simultaneous antibiotic therapy, particularly penicillin, is indicated. Sensitivity to penicillin may be overcome also by adequate dosage of cortisone or corticotropin, but it is perhaps best, should signs of infection occur, to use some other antibiotic if sensitivity to penicillin exists.

In leukemias, myelomas, lymphomas, especially Hodgkin's disease and other forms of lymph node malignancy, these preparations have been used for perhaps general supportive effect. They may be administered along with x-ray therapy or the newer drugs, especially those used in leukemia. There is little benefit to be obtained with these preparations in chronic leukemia.

In acute leukemias, the best results are obtained in children and young adults, while older persons rarely benefit. Naturally, because of the lympholytic action of these preparations, the lymphatic type of acute leukemia holds forth a better prospect of improvement. Remissions may be brought about once or twice, but thereafter the usefulness of these preparations ceases.

In other malignant processes cortisone and corticotropin have been used but, of course, not too much is to be expected. These hormones are particularly ineffective in neoplasms of connective tissue origin. In carcinoma of the breast and prostate, cortisone has been used to depress adrenal function, hoping in this way to remove steroids which have been shown to effect the growth of these tumors. If the pain of prostatic cancer is relieved by cortisone in dosages of 100 to 200 mg. a day, then total adrenalectomy might well be followed by improvement. This,

of course, should be done only after a preliminary trial of estrogens and castration.

NEPHROSIS

Hormonal therapy is of definite value in only one kidney disorder, namely, the nephrotic syndrome. This treatment depresses the adrenal cortex when cortisone is given and when corticotropin is given the adrenal cortex is temporarily stimulated, but on withdrawal it becomes hypoactive. It is because of the onset of adrenocortical inactivity that the diuresis following the period of treatment takes place.

In some instances where there is extensive fluid, especially in the abdominal and pleural cavity, paracentesis should be carried out to remove this fluid rather than waiting for the effects of hormone therapy.

During the first week or so, hormone therapy may cause a fall in the volume of the urine and actual reduction of salt output along with increase in body weight. After a week there may be an improvement in the volume of urine excreted and there may be a change in the level of the serum proteins With this improvement comes slight diuresis, and edema decreases somewhat Occasionally, considerable diuresis may occur during the latter part of a two week period of treatment. When the cortisone is withdrawn, sodium and water are released and diuresis may continue until there is no edema. In those who have a *complete loss of edema a remission may last*

Simultaneous antibiotic therapy, particularly penicillin, is indicated. Sensitivity to penicillin may be overcome also by adequate dosage of cortisone or corticotropin, but it is perhaps best, should signs of infection occur, to use some other antibiotic if sensitivity to penicillin exists.

In leukemias, myelomas, lymphomas, especially Hodgkin's disease and other forms of lymph node malignancy, these preparations have been used for perhaps general supportive effect. They may be administered along with x-ray therapy or the newer drugs, especially those used in leukemia. There is little benefit to be obtained with these preparations in chronic leukemia.

In acute leukemias, the best results are obtained in children and young adults, while older persons rarely benefit. Naturally, because of the lympholytic action of these preparations, the lymphatic type of acute leukemia holds forth a better prospect of improvement. Remissions may be brought about once or twice, but thereafter the usefulness of these preparations ceases.

In other malignant processes cortisone and corticotropin have been used but, of course, not too much is to be expected. These hormones are particularly ineffective in neoplasms of connective tissue origin. In carcinoma of the breast and prostate, cortisone has been used to depress adrenal function, hoping in this way to remove steroids which have been shown to effect the growth of these tumors. If the pain of prostatic cancer is relieved by cortisone in dosages of 100 to 200 mg. a day, then total adrenalectomy might well be followed by improvement. This,

of course, should be done only after a preliminary trial of estrogens and castration.

NEPHROSIS

Hormonal therapy is of definite value in only one kidney disorder, namely, the nephrotic syndrome. This treatment depresses the adrenal cortex when cortisone is given and when corticotropin is given the adrenal cortex is temporarily stimulated, but on withdrawal it becomes hypoactive. It is because of the onset of adrenocortical inactivity that the diuresis following the period of treatment takes place.

In some instances where there is extensive fluid, especially in the abdominal and pleural cavity, paracentesis should be carried out to remove this fluid rather than waiting for the effects of hormone therapy.

During the first week or so, hormone therapy may cause a fall in the volume of the urine and actual reduction of salt output along with increase in body weight. After a week there may be an improvement in the volume of urine excreted and there may be a change in the level of the serum proteins. With this improvement comes slight diuresis, and edema decreases somewhat. Occasionally, considerable diuresis may occur during the latter part of a two week period of treatment When the cortisone is withdrawn, sodium and water are released and diuresis may continue until there is no edema In those who have a complete loss of edema a remission may last

an indefinite period. In fact, in one of the author's patients there has been complete remission for three years, the young man having partaken in strenuous athletics.

If one does not obtain such a favorable result another course of therapy may be used, giving larger doses.

As a rule, 100 mg. to 200 mg. a day of cortisone over a period of ten to fourteen days is advocated. Children require smaller doses but rarely less than 200 mg. a day, while adults may require 300 to 400 mg. intramuscularly if the case is resistant.

Patients with the nephrotic syndrome are prone to infection and, because of the masking effect of cortisone, special attention should be shown for the appearance of any signs or symptoms of such. Cortisone depresses fever and the white count may be elevated even without infection because of cortisone administration, so that one must depend on local signs of infection or systemic manifestations, such as a feeling of illness and lack of appetite. Sudden decrease in urinary output might also herald or indicate active infection. Antibiotics, therefore, should be given in full doses. Peritonitis is one infection which may occur in nephrosis without any definite reason for its beginning.

NONENDOCRINE OR NONSPECIFIC USES OF TESTOSTERONE

The anabolic effects of testosterone preparations have been taken advantage of in patients who are not deficient in this testicular type of hormone.

As stated in previous chapters, testosterone may be quite effective in the treatment of hypopituitarism even without the use of cortisone or corticotropin. In some instances, anemia has been overcome, weight has been gained and the patient's general health maintained with doses of 300 to 400 mg. of testosterone monthly. This has been given in the form of depo-testosterone and the dose may be given once or twice a month in divided doses. Depo-testosterone in high dosage is well tolerated in a single injection, as contrasted to testosterone in suspension.

In the past I have used testosterone more generally than at the present time when cortisone or corticotropin has been available. It was frequently combined with desoxycorticosterone acetate in the treatment of Addison's disease. It does cause nitrogen retention in hyperthyroidism but since the advent of antithyroid drugs, its use is rarely indicated. Testosterone by inunction was reported helpful in the treatment of premature infants but whether this form of treatment is being continued, I do not know.

I have found it useful in ulcerative colitis, sprue and regional ileitis, and although cortisone has overshadowed its use, it would still be possible to try it where adequate food intake is not accomplished by the use of these latter two hormones. An adequate protein intake is necessary to obtain the maximum anabolic effect which may amount to 230 mg. of nitrogen a day per kilogram if such a caloric intake can be maintained.

Testosterone is also used in the treatment of metastatic

cancer of the breast. It is generally more effective in females under the age of 50 than those over 60. The dosage parenterally of testosterone propionate is from 50 to 100 mg. a day or with depo-testosterone, 200 mg. a week. The dose, of course, has to be individualized, but adequate dosage should be tried, at least in the beginning. In the premenopausal woman, castration is the preferred treatment.

The treatment of enuresis in either young boys or girls is often most difficult and all the usual measures in the psychological approach should be carried out. I have found that the sublingual or buccal administration of methyl-testosterone, 5 to 10 mg. a day, has apparently been successful in some of these cases, even in girls. It should be continued for three to six months, depending on the result obtained after a month or two. Whether this is a psychological effect or not, I am unable to determine. It was first recommended by Kugelmann in 1947.

ESTROGENS

Estrogens are used in the treatment of carcinoma of the prostate as well as carcinoma of the breast. Stilbestrol or any estrogenic preparation in adequate dosage may be used. The author has been content with stilbestrol except where it has been badly borne, and other estrogenic preparations have been substituted.

Stilbestrol in doses of 0.5 to 5.0 mg. a day may be used for nodules of the prostate which are thought to be malig-

nant, but which are small and do not require resection. Stilbestrol may be continued indefinitely if there is no increase in size, if there are no symptoms, or if the stony tumor decreases in size.

If carcinoma of the prostate is metastatic, as shown by x-ray examination and increase in the acid serum phosphatase, stilbestrol again may cause relief of pain and disappearance of symptoms and of bony lesions. It is generally accepted that perhaps the most effective method of treatment and surest chance of improvement comes after castration and the administration of estrogens.

When these procedures fail and there is increasing pain and evidence of spread, cortisone may be administered in doses of 200 mg. a day. This will suppress the adrenal cortex so that androgen-like hormones will no longer be excreted and considerable but temporary improvement may ensue. It has been said that if no improvement occurs with cortisone, total adrenalectomy is not likely to cause further improvement. Because of the better effect in reducing the 17-ketosteroid excretion by the intramuscular use of cortisone, perhaps this method of trying out the experiment is to be preferred in the long run

Stilbestrol or other estrogens in the treatment of metastatic carcinoma of the breast is more likely to be effective in the elderly patient. There is no definite rule about this, however, and if stilbestrol fails to bring about the desired result after several weeks of treatment, testosterone may then be tried In this treatment for metastatic carcinoma of the breast, stilbestrol may be given in doses up to 50

mg. a day, although 10 mg. a day often is sufficient. If the drug is not well tolerated, another preparation may be used. It is best to administer stilbestrol on retiring, along with adequate sedation, and if the patient can put up with the disagreeable nausea for a period of ten days or so it may disappear. The simultaneous use of testosterone does not appear to alter the toxic symptoms.

Roentgen therapy should not be withheld particularly if hormone therapy does not cause adequate relief of symptoms. It is during these times that cortisone may be used as an adjunct for its effect on the well-being of the patient.

CHAPTER XI

OFFICE LABORATORY TESTS

INTRODUCTORY REMARKS

A number of laboratory procedures which will aid the physician in establishing a diagnosis in endocrine disorders lend themselves to office practice. These tests will enable one to rule in or out certain conditions and plan the investigative program, whether on an ambulatory or hospitalized basis. Some of these tests may be employed as guides to therapy as well. For example, a normal Sulkowitch test for urine calcium will usually rule out hypoparathyroidism and hyperparathyroidism and will obviate the necessity of serum calcium studies in most cases. Reliable serum calcium tests are exacting procedures. The Sulkowitch test may also be employed as a guide to hytakerol, Vitamin D or hormonal therapy for metastatic carcinoma of the breast.

It should also be borne in mind that certain precautions must be observed in carrying out these tests. When the laboratory findings are in disagreement with clinical observations, one should recheck the analyses, consider

the probable sources of error, and see if all the necessary precautions have been taken in doing these studies.

TAKING BLOOD SAMPLES

I. Precautions

Syringes used for taking blood samples should be dry, as moisture will tend to produce hemolysis. The use of gauze for drying syringes should be avoided as the syringe may become chemically contaminated and erroneous values will result. Hemolysis is to be avoided as this may introduce errors in both high and low directions depending on what test is being carried out. For example, hemolysis will markedly increase the potassium and phosphorous values. To minimize hemolysis, serum should be removed from the red cells as soon as possible.

II. Fasting and Non-Fasting

Blood for serum phosphorous and potassium should be taken with the patient fasting. Blood for calcium, cholesterol, sodium and phosphatase may be taken under *any conditions.*

BASAL METABOLIC RATE

Precautions

Soda lime should be closely watched and changed either upon observing sudden increase in depth of respiratory

excursion on the graph or change in color with the new indicator limes. With the latter, the soda lime should be renewed when the color changes from orange to pink. Waiting for the pellets to change to a gray color may introduce some error. The old rule of thumb of a change of lime with every tank of oxygen does not always follow.

Rubber hose connections should frequently be checked.

False teeth should not be removed.

A high basal metabolic rate with a low pulse rate should alert the physician to search for possible technical errors.

URINARY CALCIUM (SULKOWITCH TEST)

The Sulkowitch test is a rapid simple method for the quasiquantitative measurement of the urine calcium content. If the test is to be used for diagnostic purposes, milk, acidifying agents, sulfonamides, calcium compounds and medication which would increase the urinary calcium excretion should be avoided for 48 hours before doing the test. Fluids should be controlled so that the urine output is not over a liter per day. In evaluating the calcium in a dilute urine, the specific gravity should be taken into consideration. False negatives may be obtained in urines with a gravity less than 1.005, as little buffer is present in such urines. The problem of false negatives will shortly be overcome with a test tablet or capsule containing additional buffer in the test material.*

* The tablets may be obtained through Winthrop-Stearns, 1450 Broadway, New York, New York.

The test is carried out on a clear urine. If it is turbid, it may be acidified by the addition of a few drops of 10 per cent hydrochloric or acetic acid. If it is still turbid, it may be centrifuged provided the acidity is between pH 4.5 and 5.0 (calcium compounds are precipitated at higher pHs and could be removed by centrifuging, if the urine is not acidified). Approximately an equal amount of Sulkowitch reagent* is added to about 5 cc. of urine and the turbidity is observed in about 2 minutes. The degree of turbidity is graded as 0, 1, 2, 3 and 4 plus. In the presence of large amounts of calcium, the turbidity is usually observed as the reagent is added to the urine. If there is no turbidity, there is no calcium in the sample.

EOSINOPHIL COUNT (FORSHAM)

Solutions

Solution A

Potassium oxalate	0.8 gm.
Ammonium oxalate	1.2 gm.
Distilled water q.s.a.d.	100 cc.

This solution is filtered, 0.5 cc. is placed in a small bottle or vial and evaporated to dryness. This preparation will prevent coagulation of 5 cc. of blood.

* To 2.5 gm. of oxalic acid, 2.5 gm. of ammonium oxalate and 5 cc. of glacial acetic acid, distilled water is added to make a volume of 150 cc.

Height—Weight—Age Table (Boys)

Height, Inches	5 Yrs	6 Yrs.	7 Yrs	8 Yrs	9 Yrs.	10 Yrs	11 Yrs	12 Yrs.	13 Yrs	14 Yrs	15 Yrs	16 Yrs.	17 Yrs	18 Yrs.	19 Yrs
38	34	34													
39	35	35													
40	36	36													
41	38	38	38												
42	39	39	39	39											
43	41	41	41	41											
44	44	44	44	44											
45	46	46	46	46	46										
46	47	48	48	48	48										
47	49	50	50	50	50	50									
48		52	53	53	53	53									
49		55	55	55	55	55	55								
50		57	58	58	58	58	58	58							
51			61	61	61	61	61	61							
52			63	64	64	64	64	64	64						
53			66	67	67	67	67	68	68						
54				70	70	70	70	71	71	72					
55				72	72	73	73	74	74	74					
56				75	76	77	77	77	78	78	80				
57					79	80	81	81	82	83	83				
58					83	84	84	85	85	86	87				
59						87	88	89	89	90	90	90			
60						91									
61															
62															
63															
64															
65								114	117	118	120	122	127	131	134
66									119	122	125	128	132	136	139
67									124	128	130	134	136	139	142
68										134	134	137	141	143	147
69										137	139	143	146	149	152
70										143	144	145	148	151	155
71										148	150	151	152	154	159
72											153	155	156	158	163
73											157	160	162	164	167
74											160	164	168	170	171

Prepared by Bird T Baldwin, Ph D , and Thomas D Wood, M D

From Baldwin and Wood in Duncan
"Diabetes Mellitus," published by W B Saunders Company, 1951

HEIGHT—WEIGHT—AGE TABLE (GIRLS)

Height, Inches	5 Yrs	6 Yrs.	7 Yrs.	8 Yrs	9 Yrs	10 Yrs.	11 Yrs	12 Yrs.	13 Yrs.	14 Yrs	15 Yrs	16 Yrs.	17 Yrs.	18 Yrs.
38	33	33												
39	34	34												
40	36	36	36											
41	37	37	37											
42	39	39	39											
43	41	41	41	41										
44	42	42	42	42										
45	45	45	45	45	45									
46	47	47	47	48	48									
47	49	50	50	50	50	50								
48		52	52	52	52	53	53							
49		54	54	55	55	56	56							
50		56	56	57	58	59	61	62						
51			59	60	61	61	63	65						
52			63	64	64	64	65	67						
53			66	67	67	68	68	69	71					
54				69	70	70	71	71	73					
55				72	74	74	74	75	77	78				
56					76	78	78	79	81	83				
57					80	82	82	82	84	88	92			
58						84	86	86	88	93	96	101		
59						87	90	90	92	96	100	103	104	
60						91	95	95	97	101	105	108	109	111
61							99	100	101	105	108	112	113	116
62							104	105	106	109	113	115	117	118
63								110	110	112	116	117	119	120
64								114	115	117	119	120	122	123
65								118	120	121	122	123	125	126
66									124	124	125	128	129	130
67									128	130	131	133	133	135
68									131	133	135	136	138	138
69										135	137	138	140	142
70										136	138	140	142	144
71										138	140	142	144	145

Prepared by Bird T Baldwin, Ph D , and Thomas D Wood, M D

From Baldwin and Wood in Duncan
"Diabetes Mellitus," published by W B Saunders Company, 1951

Special Diluting Solution B

Eosin (aqueous) 2%	5 cc.
Acetone	5 cc.
Distilled water	90 cc.

Refrigerate, filter before use; *prepare fresh every two weeks.*

Method

1. At 1:00 or 2.00 P.M., with or without lunch, 5 cc. of venous blood is placed in the bottle containing 0.5 cc. of the dried oxalate solution A.
2. Shake immediately and gently.
3. May be stored at 4° C. up to 12 hours.
4. Oxalated blood is drawn into a white count pipette to the 0.5 mark (with eosinophil counts below 20 per cu. mm., blood should be drawn to the 1.0 mark). The special diluting solution B is then drawn up to the 11 mark.
5. The pipette is shaken immediately and gently 50 times.
6. *Immediately* after shaking, the diluted preparation is placed in a special Levy chamber or Fuchs Rosenthal spinal fluid counting chamber 0.2 mm. in depth.
7. Wait 3 minutes.
8. Count 4 chambers and average the count.
9. The average chamber count multiplied by 6.25 equals the number of eosinophils per cu. mm. If the pipette was filled to the 1.0 mark, the final value should be divided by 2.

ASSAY OF URINARY 17-KETOSTEROIDS (CALLOW, TALBOT, SULKOWITCH)

List of Reagents

1. Concentrated hydrochloric acid C.P.
2. Methylene chloride (dichloromethane)
3. 2.0 N Sodium hydroxide C.P.
4. 0.1 N Sodium hydroxide C.P.
5. 2.5 N Potassium hydroxide in absolute alcohol (*see* 10). 9 *(nine) gm. of potassium hydroxide in 50 ml. of absolute alcohol, *filter*, check concentration by titration of 0.5 ml. with 0.1 N *sulfuric* acid. Bring within limits of 2.48-2.52 N. (*Stable only* 2-5 days in *ice box.*)
6. 0.1 N sulfuric acid standard
7. 0.01 N Sulfuric acid C.P.
8. Sodium sulfate, *anhydrous* C.P.
9. Alcohol, ethyl 95%
10. Alcohol absolute, 200 proof U.S.I.
11. Meta-dinitrobenzene purified and made up as follows:

    10 (ten) gm. of meta-dinitrobenzene is dissolved in 370 cc. of 95% alcohol.

    Warm to 40° C. Do not overheat.

    Add 50 cc. of 2 N sodium hydroxide. Cool after

* The absolute alcohol must be supersaturated to obtain a final concentration of 2.5 N KOH.

5 minutes. Do not prolong treatment with alkali. Add 1260 cc. of water in small portions with stirring. An abundant precipitate comes down. Place in ice box until it is cold. Filter cold through a Buchner funnel (medium). Wash thoroughly with water (large amount) and suck dry (2 hours to overnight).

Recrystallize twice from 60 cc. and 40 cc. *absolute* alcohol, heating to dissolve (not too hot). It may take more alcohol than these amounts for all the crystals to dissolve; use just as much more as may be necessary but not an excess of absolute alcohol. The drier the precipitate, the less alcohol is required for dissolution.

Cool immediately in tap water and then place in the ice box for a few hours each time Filter cold and suck dry for several hours to overnight, especially the final drying Final product is in long shiny needles—almost colorless.

Melting point: 90 5 to 91° C.

Melting point is not essential Purity can be tested by mixing a 1% alcoholic solution with an equal volume of 2 N sodium hydroxide. Pure material gives no color after an hour. Impure material turns red.

Other portions which may be preferred are as follows:

For 5 gm. of Meta-dinitrobenzene	*For 20 gm. of Meta-dinitrobenzene*
186 cc. of 95% alcohol	750 cc. of 95% alcohol
25 cc. of 2 N sodium hydroxide	100 cc. of 2 N sodium hydroxide
630 cc. of water	2500 cc. of water
30 and 20 cc. of absolute alcohol	120 and 80 cc. of absolute alcohol

34.5 mg. of the purified meta-dinitrobenzene crystals are dissolved in 3 ml. of absolute alcohol. This solution must be prepared fresh daily.

12. Dehydroisoandrosterone 25 mg. in 100 ml. of absolute alcohol. *This is the standard. Keep in ice box.*

This test obviously is not an office procedure but is placed here in case a reliable method is desired for a nearby laboratory.

Collection of Urine

A 24 hour specimen of urine is collected with 10 cc. of concentrated hydrochloric acid *per liter.* If the urine is assayed immediately after collection, the hydrochloric acid is not necessary.

Hydrolysis of Urine

5.0 cc. of concentrated hydrochloric acid (if no acid is added during collection, 5 5 cc. of concentrated hydrochloric acid is employed) are added to 50 cc. of urine. The acidified urine is set up with a reflux condenser, brought

to a boil and refluxed for 10 minutes. It is then chilled in an ice water bath and brought down to room temperature.

Extraction

The urine is extracted 3 times, by shaking 3 minutes each time with 30 cc. of methylene chloride in each extraction. If an emulsion forms it may be broken up by centrifugation or by chilling in ice water. The methylene chloride extracts are pooled and washed first by shaking 3 minutes each with 18 cc. of 0.1 N sodium hydroxide and then with 18 cc. of 0.01 N sulfuric acid. The extract is then washed by shaking each time with 18 ml. of distilled water until the washings are neutral to pH test paper. The neutral extract is now dried by shaking with 2 gm. of *anhydrous* sodium sulfate. Duplicate aliquots (depending on the amount of ketosteroid present) are then evaporated over a stream of air in a water bath. The colorimetric reaction is now carried out on the dry residue.

Colorimetric Reaction

1. 2 blanks 0.2 ml. of absolute alchohol
2. 3 standards 0.2 ml. of dehydroisoandrosterone standard in absolute alcohol
3. Unknowns add 0.2 ml. of absolute alcohol to each tube. To all tubes add the following:
   a. 0.2 ml. of meta-dinitrobenzene solution in absolute alcohol
   b. 0.2 ml. of 2.5 N alcoholic potassium hydroxide

Stopper, shake and place in dark in a constant temperature water bath at 25° C. for 105 minutes. Immediately thereafter add 10 cc. of 95% alcohol to each tube, diluting in the order in which the tubes are to be read. Mix by inversion; read on colorimeter within 10 minutes with both a green (approximately 540μμ) and a blue (approximately 420μμ) filter.

CALCULATION AND CORRECTION FACTOR

The correction factor of Talbot and associates for interfering chromogens is employed.

$$\frac{Ki \times G - B}{Ki - Ks} = C \text{ corrected reading}$$

G (E_g) is the extinction coefficient for solution of urine extract minus blank (meta-dinitrobenzene reaction products) for the green filter.

B (E_b) is the same coefficient for the blue filter.

Ki is the ratio of $\frac{E_b}{E_g}$ for interfering chromogens (nonketonic substances in urine)

Ks is the ratio of $\frac{E_b}{E_g}$ for pure crystalline 17-ketosteroid.

Theoretically, these factors should be determined by actual measurement with the operator's colorimeter For practical purposes one may use Talbot's figures: $\frac{E_g}{E_b} = 2.2$ This is the inverse of K_s which is $\frac{E_b}{E_g}$ for pure 17-ketosteroid.

$\frac{E_g}{E_b} = 0.6$. This is the inverse of Ki which is $\frac{E_b}{E_g}$ for interfering chromogens.

Therefore the formula will read:

$$\frac{\frac{1}{.6} \times (G) - B}{\frac{1}{6} - \frac{1}{2.2}} = \frac{1.67 \times G - B}{1.67 - 0.45}$$

$$= \frac{1\ 67 \times G - B}{1.22} = C$$

The final calculation equals mg. 17-ketosteroids and is made as follows:

$$\frac{C}{G \text{ std} \begin{pmatrix} \text{Extinction coef.} \\ \text{Std. minus} \\ \text{Ext. blank in green} \end{pmatrix}} \times \frac{50}{1{,}000} \times \frac{90}{\text{Vol. extract evaporated}}$$

$$\times \frac{\text{Total volume of urine}}{\text{Vol. of urine extracted}}$$

Example

Colorimetric reading	*G* (Extinction coef. or logarithm)	Std.	154
" "	*G* Blank		40
" "	*G* Unknown		169
" "	*B* Unknown		177
" "	*B* Blank		64
Total volume urine			1120 ml
Volume extract evaporated			5 cc.

$$\text{Corrected reading} = \frac{1\ 67\ (169 - 40) - 177 - 64}{1.22}$$

$$= \frac{1.67\ (129) - 113}{1.22} = \frac{215 - 113}{1.22}$$

$$= \frac{102}{1.22} = 83.6$$

$$\text{Mg. 17-ketosteroid} = \frac{83.6}{154 - 40} \times \frac{50}{1{,}000} \times \frac{90}{5} \times \frac{1120}{50}$$

$$= \frac{83.6}{114} \times 20.16$$

$$= 14.8$$

LYMPHOCYTES

DIFFERENTIAL COUNTS FOR MEASUREMENT OF TOTAL NUMBER OF LYMPHOCYTES

The usual procedure of counting 100 cells in a smear to determine the total number of lymphocytes may introduce a considerable error. A total of 500 cells should be counted from different parts of the slide.

SPERM COUNTS *

Reagents

Greenberg's stain for spermatozoa
Locke-Ringer's solution
Alcohol-ether
(equal parts of each) mixture

Sampling

The semen is collected either by masturbation, coitus interruptus, or Doyle spoon, placed in a clean jar and brought to the laboratory *within one hour* after collection.

* Adapted from Harris, "Human Fertility."

Care should be exercised that the specimen is not chilled in transportation. Times of collection, arrival at laboratory, and assay should be noted.

Procedure

(1) Measure the volume with a syringe

(2) Mix by stirring with a wooden applicator and arbitrarily evaluate viscosity in so doing

(3) Place a drop of semen on a glass slide, cover with cover slip and observe under high dry for following:

  (a) Motility, degree of
  (b) RBC, WBC and epithelial cells
  (c) Crystals
  (d) Spermatocytes
  (e) Spermatids
  (f) Clumping
  (g) Mucus threads, debris, etc.

(4) Counting: The mixed semen is drawn up to the 0.5 mark in a WBC pipette and diluted to the 1.1 mark with Locke-Ringer solution, and shaken. The count is made using the RED cell part of the hemacytometer—using the four outside and middle square (total of 80 boxes). The chambers on each side are filled and the average of the two is taken. The active and inactive sperm are counted separately. To obtain the number of sperm per cc., add six zeros to the number of sperm in the five large squares (averaging both chambers first).

(5) Smear: Place a drop of semen on the end of a glass slide and spread evenly by drawing with another slide. Drop immediately into the equal parts alcohol-ether mixture (fixative, see above). Flood the slide with Greenberg's stain for spermatozoa. After standing with the stain for 15 minutes, wash under tap water and blot. One hundred sperm cells are counted with either the high dry or oil immersion objective under the microscope and the percentage of abnormal sperm are determined. The abnormal sperm may be classified as follows:

(a) Amorphous
(b) Round heads
(c) Pin heads
(d) Giant heads
(e) Tapering forms
(f) Coiled tails
(g) Duplex heads
(h) Duplex tails
(i) Cytoplasmic appendages

VAGINAL SMEARS
IODINE VAPOR TECHNIQUE (MACK)

Method

1. Moistened cotton swab is inserted and rotated firmly against the vaginal wall.

2. Smear is made by rolling swab on glass slide.

3. After slide is dry, it is stained by placing it face down over a shallow dish containing Lugol's solution. (It does not touch the solution.)

4. Iodine vapor stains the glycogen in the vaginal cells within 2 or 3 minutes.

5. Smear is examined under microscope.

Interpretation

If most epithelial cells are stained brown, there is a good estrin effect. If none are stained, there is no estrin. Intermediate degree of staining indicates less estrin effect. Most significant, therefore, is the fully stained smear or the one which does not stain at all.

TABLE 1

NORMAL HEIGHT—MALES

(Without Shoes) From Burgess Charts

Age in Years	AVERAGE HEIGHT 50 per cent Curve (Inches)	UPPER LIMITS 99 per cent Curve (Inches)	LOWER LIMITS 1 per cent Curve (Inches)
1	31.4	33.6	26.9
2	34.4	38.4	30.8
3	37.6	41.2	33.1
4	40.4	44.2	36.0
5	42.8	47.4	38.2
6	45.0	49.8	40.3
7	47.1	51.6	42.3
8	49.1	54.0	44.2
9	51.1	55.8	46.0
10	53.0	58.2	47.6
11	54.7	60.3	49.2
12	56.4	62.9	50.4
13	58.6	65.8	52.0
14	61.0	68.4	53.5
15	63.6	71.8	55.2
16	65.6	73.1	58.0
17	66.8	73.5	59.5
18	67.2	73.7	60.7
19	68.1	73.8	61.0

Height age is determined [illegible]
normal average height colun [illegible]
second column marked 99 pei [illegible]
cate that 99 per cent of males are shorter than the given value for age, and in the column marked 1 per cent curve, values indicate that 99 per cent of boys are above this height. In interpreting height age, attention should be paid to height of

other members of family. Rate of growth from year to year is more important than height age unless bone age is at marked variance from actual (chronological) age. To change measurement to centimeters, multiply inches by 2.54.

TABLE 2

NORMAL HEIGHT—FEMALES

(Without Shoes) From Burgess Charts

Age in Years	AVERAGE HEIGHT 50 per cent Curve (Inches)	UPPER LIMITS 99 per cent Curve (Inches)	LOWER LIMITS 1 per cent Curve (Inches)
1	30.0	33.4	26.6
2	34 0	37 8	30 0
3	37.2	41.4	33 2
4	40.0	44.3	35.6
5	42.4	47 0	38 0
6	44.6	49.4	39.8
7	46 8	51.6	41 8
8	48.8	53 6	43.6
9	50.8	55.8	45 4
10	52.6	58.0	47.2
11	54.8	60 8	48.8
12	57.0	63.8	50 4
13	59.4	66.4	52.6
14	61.2	67.6	54.6
15	62.0	68.0	56 2
16	62.6	68.2	57.0
17	62.7	68.3	57.3
18	62.8	68 3	57.3

Height age is determined by matching observed height with normal average height column and reading off age to left. In second column marked 99 per cent curve, the values given indicate that 99 per cent of girls are shorter than the given value

for age, and in the column marked 1 per cent curve, values indicate that 99 per cent of girls are above this height. In interpreting height age, attention should be paid to height of other members of family. Rate of growth from year to year is more important than height age unless bone age is at marked variance from actual (chronological) age. To change measurement to centimeters, multiply inches by 2.54.

TABLE 3

DESIRABLE WEIGHTS FOR MEN OF AGES 25 AND OVER

Weight in Pounds According to Frame (as ordinarily dressed)

Height (with shoes on) Feet	Inches	Small Frame	Medium Frame	Large Frame
5	2	116-125	124-133	131-142
5	3	119-128	127-136	133-144
5	4	122-132	130-140	137-149
5	5	126-136	134-144	141-153
5	6	129-139	137-147	145-157
5	7	133-143	141-151	149-162
5	8	136-147	145-156	153-166
5	9	140-151	149-160	157-170
5	10	144-155	153-164	161-175
5	11	148-159	157-168	165-180
6	0	152-164	161-173	169-185
6	1	157-169	166-178	174-190
6	2	163-175	171-184	179-196
6	3	168-180	176-189	184-202

This table is based on numerous Medico-Actuarial studies of hundreds of thousands of insured men and women.

Printed by permission of the Metropolitan Life Insurance Company.

TABLE 4

DESIRABLE WEIGHTS FOR WOMEN OF AGES 25 AND OVER

Weight in Pounds According to Frame (as ordinarily dressed)

Height (with shoes on) Feet	Inches	Small Frame	Medium Frame	Large Frame
4	11	104-111	110-118	117-127
5	0	105-113	112-120	119-129
5	1	107-115	114-122	121-131
5	2	110-118	117-125	124-135
5	3	113-121	120-128	127-138
5	4	116-125	124-132	131-142
5	5	119-128	127-135	133-145
5	6	123-132	130-140	138-150
5	7	126-136	134-144	142-154
5	8	129-139	137-147	145-158
5	9	133-143	141-151	149-162
5	10	136-147	145-155	152-166
5	11	139-150	148-158	155-169

This table is based on numerous Medico-Actuarial studies of hundreds of thousands of insured men and women.

Printed by permission of the Metropolitan Life Insurance Company

FROG TEST FOR PREGNANCY

(Robbins, Parker, and Hodgson)

The frog test for pregnancy lends itself to office practice if a refrigerator is available for maintaining the animals in a state of hibernation.

Materials Required

I. Animals:
  a. African female frogs (Xenopus laeris)
  b. North American male frogs (Rana pipiens)

II. Reagents:
  a. Nitrazine paper
  b. 0.04% bromcresol green
  c. 0.04% phenol red
  d. 10% HCL
  e. 20% HCL
  f. 0.1% NaOH
  g. 20% water suspension (acid washed u. infra*) "Kaolin Washed Powder" * (American Standard)

SELECTION AND CARE OF FROGS

In this country the male North American frogs (Rana pipiens) are more readily available and for the sake of brevity the presentation will be limited to the use of this species. The males are distinguished from the females by their large pigmented thumbs, inflated air sacs, and ability to croak.

* The "Kaolin Washed Powder" (American Standard) obtainable from the J T. Baker Co., Phillipsburg, N J., may be employed without further treatment, whereas other kaolin preparations may require acid washing before they may be used.

PROCEDURE

The frogs are kept in a refrigerator maintained between 5 and 10° C. (41 to 50° F.). The frogs must be preserved in a state of hibernation and are *not* to be given *food* of any kind. The water in the bottom of the pan is changed daily.

CONTROL OR BLANK

After weighing the frog, he is permitted to thaw out at room temperature for a short interval and the frog's urine is checked for absence of sperm. Urine may be obtained by pressing the animal on a glass slide or flexing his thighs, which stimulates him to void. Should this method of stimulation be ineffective, the urine may be obtained by insertion of a capillary tube* or pipette. The urine is examined microscopically for sperm.

PREPARATION OF URINE SAMPLE

Only urine with a specific gravity of 1.010 or greater may be used. A fasting morning sample is ideal, and whenever practical, patients should be advised to restrict fluids after the evening meal, the night before bringing in the sample. The urine is acidified with 10 per cent HCL

* The tip of a medicine dropper may be drawn out over a micro-burner for this purpose.

added dropwise to a pH of approximately 5.0 and filtered.

PREPARATION OF SERUM

Twenty cubic centimeters of whole blood (*no* anticoagulant), is allowed to clot, centrifuged, and the serum is removed.

INJECTION OF FROGS

One cubic centimeter of urine or serum per 10 gm. of frog is injected into the peritoneal or dorsal lymph sac of the frog with a hypodermic needle. Application of rubber cement or Varniton* at the margin of the needle hub and the syringe will prevent possible leakage of the injectable material at this junction.

EXAMINATION OF FROG'S URINE AFTER INJECTION AND INTERPRETATION

The frog's urine is obtained (v. supra) and examined for sperm thirty minutes to three hours after injection of the material. Positive tests usually appear within thirty to fifty minutes after injection. A negative result does not rule out pregnancy. The urine may be concentrated by one of the "kaolin adsorption"** procedures, whereby 1

* Varniton may be obtained at the Varniton Co., 416 N. Varney Street, Burbank, California.

** 100 ml. (if this amount is not available*** the volume is measured and made up to that of 100 cc. with distilled water) is placed in a

cc. of urine concentrate = a 20 fold increase in chorionic gonadotropins. However, this technique is beyond the scope of the average office laboratory, but may be feasible in the more elaborate set-ups found in the group practice laboratories.

---

graduated cylinder, 5 drops bromcresol green as an indicator are added and the pH is adjusted to 4 0 with 20 per cent HCL.

*** A volume of less than 50 cc. of urine is inadequate and should not be used 5 cc. of a 20 per cent aqueous suspension of the "special kaolin washed powder—Am. Std." or acid washed kaolin are added to the acidified urine. The mixture is agitated either in a mechanical shaker or by inverting twelve times when done manually. The cylinder then is allowed to stand until the kaolin has settled down to a volume of 15 to 20 cc. and the supernatant fluid is then removed by vacuum aspiration and discarded. The remaining kaolin suspension is then centrifuged for five minutes and the supernatant discarded. To the packed kaolin residue 5 cc. of 0 1 N NAOH are added and thoroughly mixed

Complete dispersion of the alkali and the kaolin is essential for *ultimate election* of the *chorionic gonadotropin* The mixture is then spun at 2,500 to 3,000 RPM for five or more minutes until the supernatant becomes clear. The latter is poured off into a *graduated* centrifuge tube containing 2 drops 0 04 per cent phenol red (if phenolphthalein is used it must be made up fresh) and 20 per cent HCL is added dropwise with agitation until the indicator changes from red to orange. The total volume is then noted on the graduated centrifuge tube One cubic centimeter of this concentrated urinary extract is injected either intraperitoneally or in the dorsal lymph sac and the frog's urine is examined in the same manner as described in the previous section. In doing a quantitative assay for diagnostic purposes, such as the presence of remnants of a chorioepithelioma, the following formula is utilized to give the degree of concentration of the gonadotropin by the kaolin

$$\frac{\text{Volume of urine added} \times 5}{\text{Final volume in graduated centrifuge tube}}$$

INDEX